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Biologically active naturally produced and synthetic compounds often feature chiral centers and heteroatoms. The inclusion of these heteroatoms in cyclic motifs such as lactones and lactams with specific stereochemistry is common. While naturally produced compounds can be isolated, often the small quantities that can be collected are not sufficient for extensive testing or commercial production. This yield issue can be overcome by total synthesis of the natural compound. Additionally, the total synthesis of complex bioactive compounds allows for the derivatization of the structure, which can be used to improve efficacy or better understand the mechanism of action. To effectively produce natural products efficient methodologies for enantioselectively synthesizing complex motifs, such as spirocycles and bicycles, are needed.

The research described in this thesis applies the asymmetric synthetic method of desymmetrization to the synthesis of enantioenriched bicyclic and spirocyclic motifs. The symmetric achiral starting materials for both projects are synthesized and then reacted with chiral phosphoric Brønsted acid catalysts to cause enantioselective intramolecular cyclization. While the attempts to form the bicyclic lactone have yet to produce detectable desired product, the work done has shown the ability to synthesize starting materials and given insight into possible productive modifications. The spirocyclic work has expanded the substrate scope started previously in the Petersen group and sets the foundation for a mechanistic pathway study for the spirocyclic formation. The application of the desymmetrization methodology to an increasing number of symmetric substrates explores the wide scope of this reaction mechanism.

FORMATION OF BICYCLES AND SPIROCYCLES VIA DESYMMETRIZATION

by

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Approved by

_____
Committee Chair

To my family for their endless belief in my abilities, to Emma for 11 years of amazing support and adventures, to Mary for keeping me sane and making me leave the house, to Sean for helping me pass Biochemistry II and being pretty awesome all of the time, to Michael for loving organic chemistry as much as I do, to Haley for sticking with me for all these years, and to my fellow students in the chemistry department for making this crazy science life fun.

APPROVAL PAGE

This thesis written by Kyla J. Stingley has been approved by the following committee of the Faculty of The Graduate School at the University of North Carolina at Greensboro.

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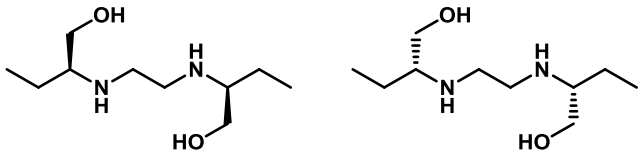
CHAPTER I

INTRODUCTION

1.1 Chirality

The discovery and synthesis of small molecules with biological activity is a major focus for many branches of chemistry. While the structure of such molecules can vary widely, there are certain aspects which play a large role in many bioactive compounds; the presence of heteroatoms and chiral centers are two such aspects. Asymmetric centers particularly result in a variety of synthetic difficulties and complex biological activity effects. A traditional chiral center is an atom with 4 differing substituent groups and the fixed geometric configuration of these groups will determine the activity of that center or compound. Each chiral center has a nonsuperimposable mirror image which represents the opposite configuration of those same groups. When configurations of all of these stereocenters are reversed the corresponding compound is the enantiomer, while if some, but not all, of the configurations are changed the resulting molecule is a diastereomer of the original. Diastereomers are chemically inequivalent, meaning they can be distinguished and separated in achiral environments. Conversely, enantiomers are chemically equivalent in achiral environments and only possess differing activity when interacting with a chiral agent, making them much more difficult to purify or synthesize enantioselectively. The geometric conformation of the molecule can have a dramatic effect on the way it interacts with biological systems due to the fact that the majority of enzymes and active sites which bind to the small molecule are chiral in nature. Due to the differing activity of diastereomers or enantiomers of the same

compound, the synthesis of enantioenriched motifs and compounds is of great importance in the production of drugs.



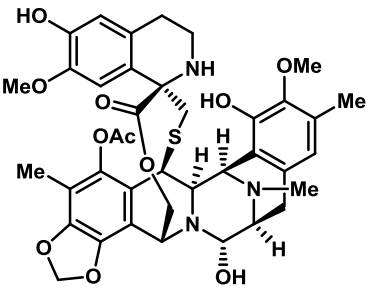
D-ethambutol (1) L-ethambutol (2)

Figure 1. Enantiomers of Ethambutol

The compound ethambutol (Figure 1) features both aspects, as well as highlighting the potential danger of using a mix of enantiomers in vivo. The activity of ethambutol against tuberculosis was first discovered in 1961 by J.P. Thomas and coworkers during a screen of synthesized small molecules.[1,2] While this initial activity study identified D-ethambutol (**1**) as the enantiomer responsible for most of the therapeutic effects, the toxicity of L-ethambutol (**2**) was not established and so the more easily synthesized racemic mixture was used for the initial clinical trials.[1,2] These clinical trials, reported by Carr and Henkind, resulted in serious toxic ocular symptoms, causing blindness or severe visual impairment in nearly half of the patients.[2,3] Given these damaging side effects, the enantiomers were separated and the therapeutic D-ethambutol was used in subsequent trials.[2] Through multiple studies of the D-enantiomer it was determined that the toxicity was predominantly due to the L-ethambutol, and so D-ethambutol was used as a single enantiomer.[2,4,5] There is still debate over the toxicity of D-ethambutol, specifically the severity and occurrence of the ocular side effects reported, but it is undoubtedly to a lesser degree than the racemic mixture.[5]

The selection for enantiopure forms of a compound not only applies to synthetic small molecules, but natural products as well. While a wide number of compounds

isolated from natural sources demonstrate biological activity, the purification process of a single compound from an extract can be tedious and difficult, with a complex mixture of compounds often present. Additionally, the yield of a single compound from an extract can be extremely small, requiring a large quantity of natural material to produce a usable amount of the desired compound. One method to circumvent this issue is the semisynthesis of a compound, using a more abundant natural product precursor as starting material.[6] This approach greatly shortens the synthesis of a complex natural product while requiring a much more reasonable amount or type of biomass. Another is total synthesis, which uses commercially available compounds to synthesize the natural product. While this method can be lengthy, it also gives complete synthetic control over the molecule and does not rely on any biological source.



Ecteinasciden 743 (3)
(Yondelis)

Figure 2. Natural Product Ecteinasciden 743

Isolated from the colonial tunicate *Ecteinascidia turbinata* in 1986, ecteinascidin 743 (Figure 2) is one biologically active natural product which greatly benefitted from a semisynthesis approach.[6,7] Now known by the pharmaceutical name Yondelis, ecteinascidin 743 is the most abundant of six ecteinascidin compounds isolated from the same colonial tunicate with a yield of 0.0001%.[6,7] Although it demonstrated great activity

against leukemia cell lines with an IC_{50} of 0.5 ng/mL, the extremely low yield restricted ecteinascidin 743 from extensive biological activity testing.[6,7] Initially a total synthesis was designed by Corey et. al. which took a total of 13 steps and produced derivatized analogs which also displayed biological activity, though the original compound remained the most potent.[8,9] This synthesis allowed greater access to the natural product, but was improved upon by using cyanosafracin B (**5**), a fermentation product of the bacteria *Pseudomonas fluorescens* which can be harvested for starting material on a kilogram scale.[9] This semisynthesis is completed in 10 steps, still allowing for derivatization, and has enabled the large scale production of ecteinascidin 743.[6,9] With availability no longer an issue, ecteinascidin 743 moved on to extensive clinical trials, eventually making it onto the drug market as Yondelis.[6]

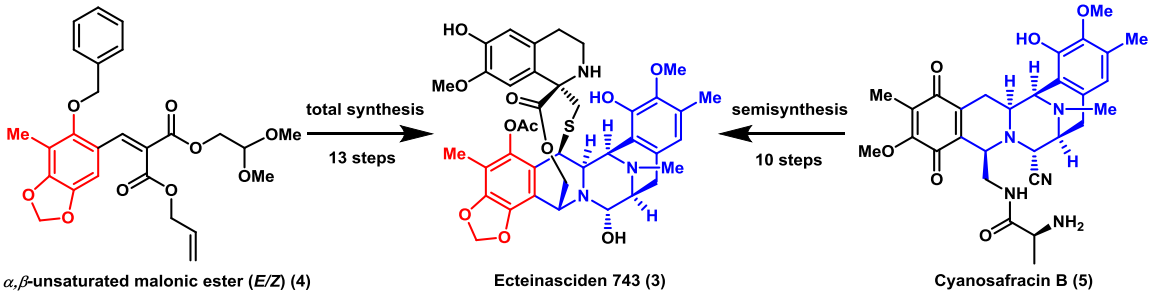


Figure 3. Starting Materials for the Total and Semisynthesis of Ecteinascidin 743

As with many natural products, ecteinascidin 743 exists as a single enantiomer, and so its total synthesis required the application of enantioselective synthetic techniques.[8,9] While the total synthesis was later improved upon by the use of naturally made complex starting material, the ability to synthesize ecteinascidin 743 allowed for continued biological testing and derivatization.[8,9] The semisynthesis of ecteinascidin 743 decreased the number of steps and the complexity of the process due to the numerous

stereocenters already set in the natural precursor cyanosafricin B. As shown in Figure 3, cyanosafricin B possesses 6 of the 8 stereocenters of the final product ecteinascidin 743, while the starting material (**4**) made in 1 step from commercially available compounds for total synthesis possesses none. Thus, both biologically active compounds discussed serve as clear examples of the need for facile, diverse enantioselective synthetic strategies.

1.2 Asymmetric Synthesis Strategies

To produce enantioenriched materials for novel small molecules or the total synthesis of natural products, asymmetric synthetic techniques are vital and expanding. While there are many varied approaches to this task, kinetic resolutions and desymmetrizations are two major types.

1.2.1 Kinetic Resolution

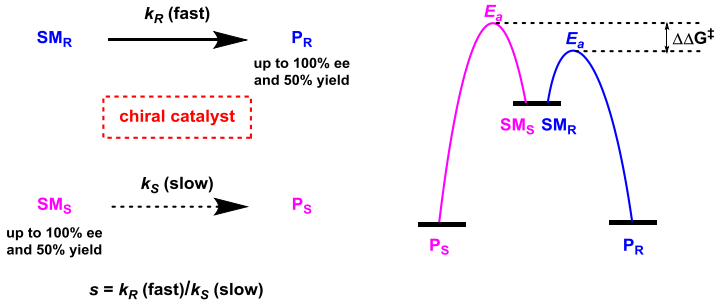


Figure 4. General Schematic of Kinetic Resolution

The strategy of kinetic resolution is an important option for enantioselective synthesis. The term includes an array of specific variations allowing for its wide applicability, but all incorporate the same basic methodology.[10,11] The basis of all kinetic resolutions is shown in Figure 4; the exposure of racemic starting material (SM) to a chiral agent allows for the separation of the starting material enantiomers (SM_R and SM_S)

due to the difference in the rates of the reaction (k_R and k_S) to form the product (P).[10,11] The difference in the activation energies for the two enantiomers at the rate determining step ($\Delta\Delta G^{\ddagger}$) is used to determine the relative rates of reaction, and, therefore, which enantiomer will be converted to the product more quickly. This rate disparity allows for the ideally complete conversion of one enantiomer of starting material to product before the other enantiomer, producing both enantioenriched product of the faster enantiomer and enantioenriched starting material of the slower. The degree of selectivity or difference in reaction rates for the two enantiomers of starting material is expressed by the selectivity factor (*s*). As shown in Figure 4, the selectivity factor is the ratio of the k_{fast} to k_{slow}, a larger number indicating a larger rate difference.[10,11] This value allows for the comparison of kinetic resolutions using differing substrates and reactions based on stereoselectivity and energy difference.[10,11] Ideally, this method can produce the faster reacting enantiomer product and the slower reacting enantiomer recovered starting material in up to 100% enantiomeric excess and 50% yield for each, considering the initial racemic mixture contains 50% of each enantiomer. Overall the yield of enantioenriched material is up to 100%, and the enantioenriched starting material could be converted to enantioenriched product in a subsequent reaction. The benefits of this method are its versatility, and ability to be applied in combination with other enantioselective synthetic techniques, with the maximum of 50% yield of enantioenriched product its main detriment.[10,11]

1.2.2 Desymmetrization

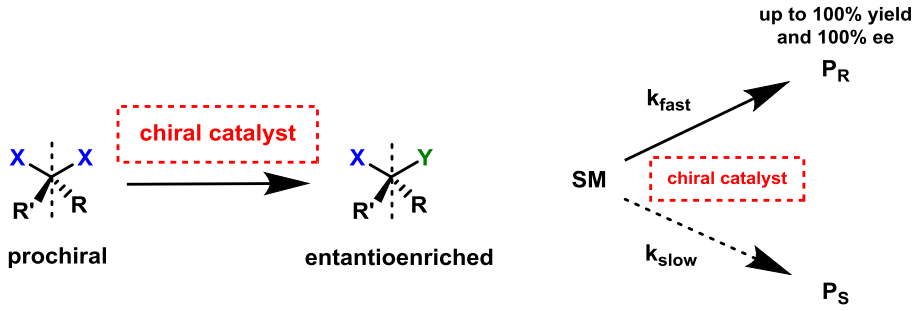


Figure 5. General Schematic of Desymmetrization

Desymmetrization is a method of enantioselective synthesis which, unlike kinetic resolution, can produce products with up to 100% yield and 100% enantiomeric excess. The basis of this difference is the achiral nature of the starting material, which features two enantiotopic groups at the prochiral center and a plane of symmetry (Figure 5). When the starting material interacts with the chiral catalyst, one of the enantiotopic groups is altered, resulting in the establishment of a chiral center. Similar to kinetic resolution, the enantioselectivity of this transformation is established by a rate difference, in this case between the 2 different configurations the prochiral starting material can form when interacting with the chiral agent. Due to the absence of chirality in the starting material, there is the potential for all the starting material to be converted through the favorable interaction (k_{fast}) to enantioenriched product.

1.3 Organic Chiral Brønsted Acid Catalysts

The use of organic compounds to catalyze asymmetric synthesis is often preferable to the metallic and enzymatic alternatives for many reasons. While metal catalysts require inert storage and careful handling to avoid deactivation, organocatalysts can often be stored in non-inert conditions.[12,13] The generally lower

prices as compared to metal catalysts for many organocatalysts is another benefit, as well as the more environmentally friendly nature of the carbon-based catalysts.[12,13] Handling difficulties apply not only to metallic but enzymatic catalysts as well.[13,14] In addition, enzymatic catalysts often suffer from limited versatility and difficulty in recovery.[13,14] These factors have led to a dramatic increase in organocatalytic usage and development in recent years.[12,13,15–17]

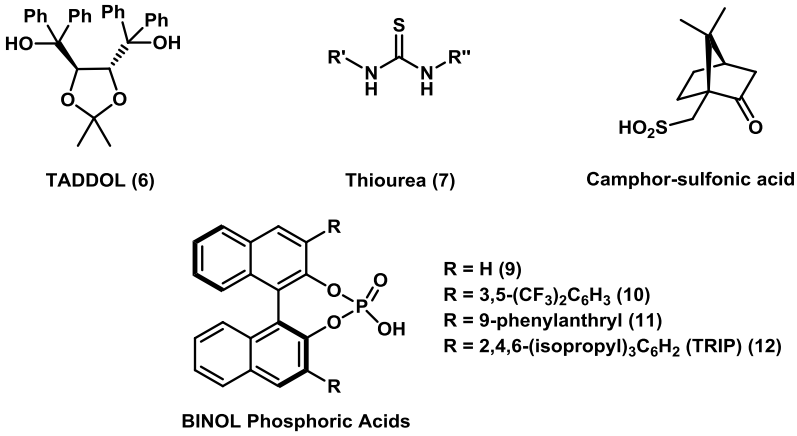


Figure 6. Chiral Hydrogen Bonding and Brønsted Acid Organocatalysts

Within this growing field of chiral organocatalysis is the branch of chiral Brønsted acid catalysts. As one of the most newly developed branches, the popularity and development of chiral Brønsted acid catalysts was first spurred by the 2004 application of chiral BINOL phosphoric catalysts to Mannich type reactions by the Akiyama and Terada groups.[18–20] Since then, Brønsted acid catalysts have been applied to a variety of asymmetric reactions and the diversity of catalyst structure and acidity allows for wide scope of applications.[15–17,20,21] Examples of commonly used Brønsted acid catalysts are based on a TADDOL (**6**), camphor sulfonic acid (**7**), thiourea (**8**), or BINOL phosphoric acids (**9-12**) scaffold (Figure 6).

1.4 Previous Work in the Petersen Group

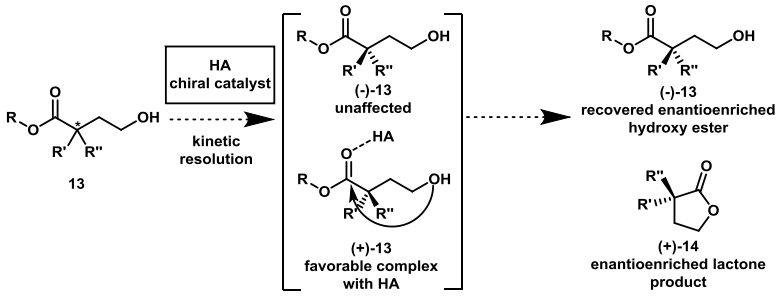


Figure 7. Kinetic Resolution of α-Hydroxy Esters

The cumulative work done over previous years by members of the Petersen group has utilized each of the discussed asymmetric synthesis concepts. In 2013 the synthesis of enantioenriched hydroxy esters (**13**) through kinetic resolution was reported (Figure 7).[22] This method used the aryl-substituted BINOL phosphoric acid TRIP catalyst (**12**) to enantioselectively cyclize hydroxy esters to their corresponding lactones, producing enantioenriched hydroxy ester and lactone products.

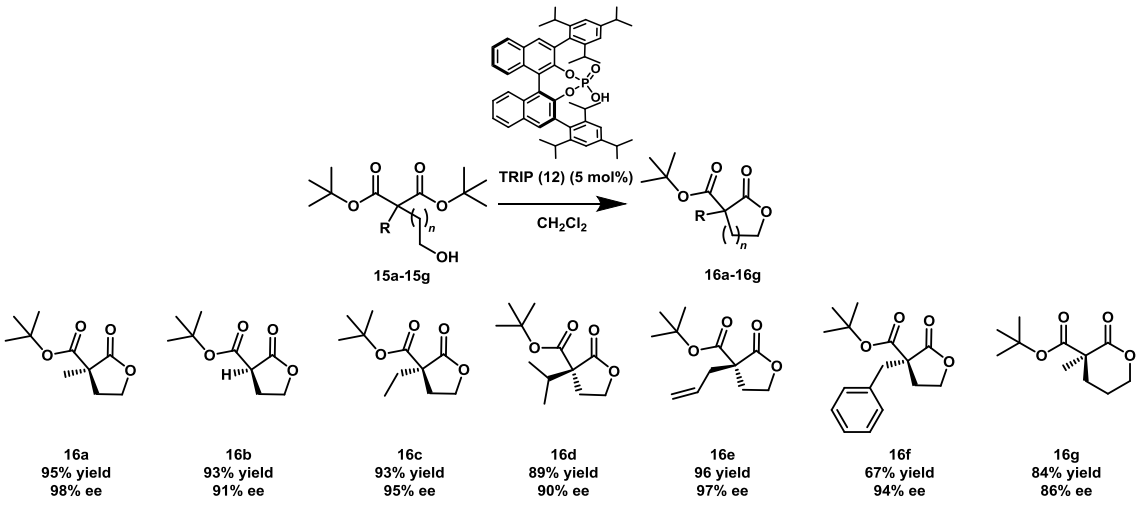


Figure 8. Synthesis of Enantioenriched Monocyclic Lactones via Desymmetrization

A paper published in 2014 utilized the same BINOL-derivative phosphoric acid catalyst to complete the desymmetrization of prochiral diesters (**15a**-**15g**) to enantioenriched lactones (**16a**-**16g**).[23] The substrate scope of this work, shown in Figure 8, featured the synthesis of compounds incorporating a variety of substituents, including alkyl, aryl, and allylic groups, in good to great yields and enantiomeric excess.[23] This more recent publication served as the direct precursor to the desymmetrization work discussed in the following chapters. In both the desymmetrization and kinetic resolution the activation of the BINOL phosphoric acid catalyst involves both acidic and basic coordination (Figure 9). The carbonyl oxygen of the substrate is activated through hydrogen bonding or full hydrogen transfer of the catalyst's hydroxyl hydrogen, while the hydroxyl group of the substrate coordinates similarly to the double bonded oxygen of the catalyst. This double activation encourages the intramolecular nucleophilic attack at the carbonyl carbon at both the nucleophilic and electrophilic groups. This attack forms the lactone product and causes the compound to dissociate from the catalyst. The BINOL catalyst's axial chirality and large, bulky substituents enantioselectively direct the cyclization reaction.[15,22,23] Our hypothesis is that the enantiomer or configuration with less steric clashing between reactant and chiral substituents will bind more favorably to the catalyst, with that enantiomer then progressing to enantioenriched product.

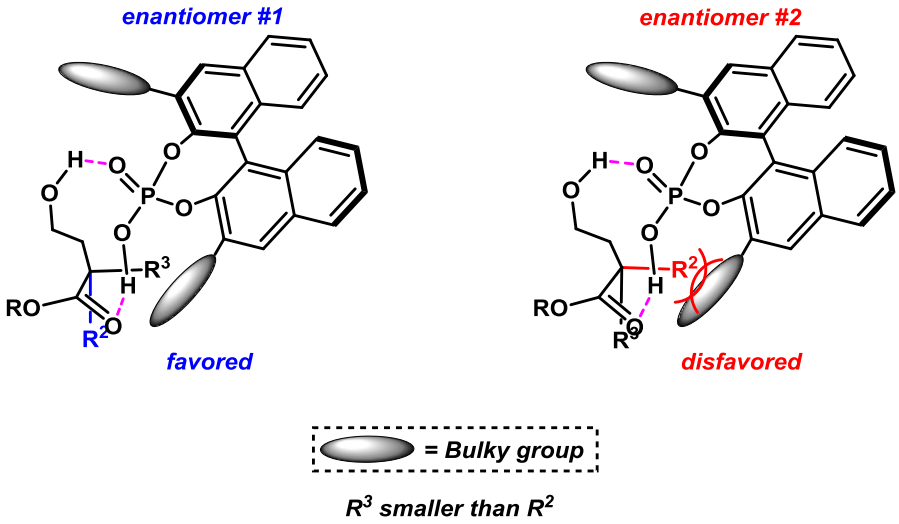


Figure 9. Proposed Activation of BINOL Catalyst

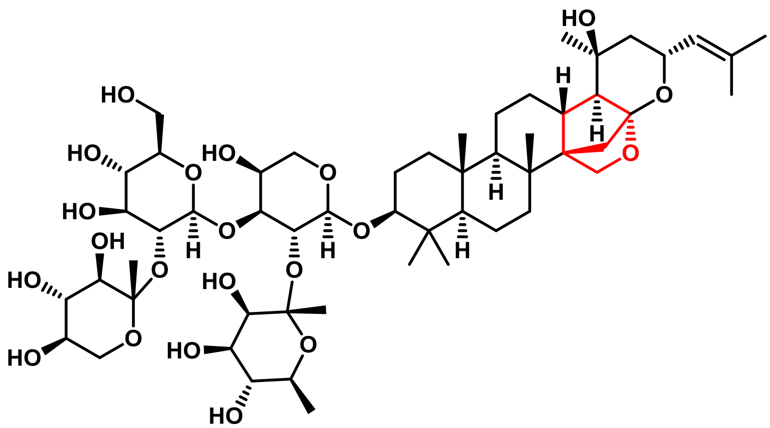
1.5 Conclusion

The work discussed in the following sections will seek to utilize the desymmetrization method of asymmetric synthesis to produce compounds containing all-carbon chiral centers enantioselectively. These investigations will expand on the previous work done in the Petersen lab and further explore the applications of chiral Brønsted acid catalyzed desymmetrizations. The successful synthesis of meso starting material for bicyclic and spirocyclic lactone formation is detailed, as well as attempts to produce the desired enantioenriched compounds.

CHAPTER II

ASYMMETRIC SYNTHESIS OF ENANTIOENRICHED BICYCLES

2.1 Introduction

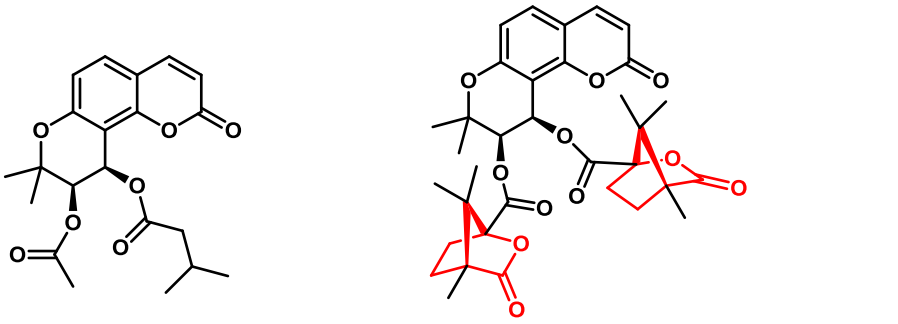


Jujuboside B (17)

Figure 10. Natural Product Jujuboside B

Bicyclic lactones and ethers are motifs found in a variety of biologically active natural and synthesized compounds. Compounds **17** and **19**, found in Figures 10 and 11, are two examples of complex molecules containing this motif and demonstrate the wide-reaching applications. Jujuboside B (**17**) is a natural product extracted from the mature seed of *Zizyphus jujube Mill of Rhamnaceae*, Zizyphi Spinosi Semen (ZSS).[24] The dried seed has been a part of traditional Chinese medicine for centuries, used to treat conditions for amnesia to insomnia, and containing a variety of active compound families such as flavonoids, alkaloids, and jujuboside B's family, saponins.[24,25] Extracted and elucidated by x-ray crystallography in 1978, jujuboside B is one of the major

sapoinins contained in ZSS and has shown biological activity as an isolated compound toward tumor formation suppression and vascular tension reduction, the latter a benefit which has only recently been investigated in depth.[24,25]



(+)-suksdorfin (18)

3',4'-di-O-(-)-camphanoyl-(+)-cis-khellactone (DCK) (19)

Figure 11. Natural Product Suksdorfin and Synthetic Derivative DCK

Compound **19**, 3',4'-di-O-(-)-camphanoyl-(+)-cis-khellactone (DCK), is a synthetic analog of the natural product suksdorfin (**18**), derivatized due to the original compound's high activity in HIV-1 replication inhibition.[26] As shown in Figure 11, DCK maintains suksdorfin's core structure while substituting alkyl chains for bicyclic lactone motifs, a change which decreased the EC_{50} from 1.3 µM to 0.00041 µM.[26] Following this initial total synthesis in 1994 there have been numerous publications focused on the synthesis of derivatives of DCK, altering each of the components of the molecule to determine the importance of each.[27] In addition to determining the large difference in reactivity of the diastereomers, the inclusion of at least one bicyclic lactone motif in the compound proved to be critical to the bioactivity.[28–30]

Despite their demonstrated biological activity and applications in synthetic analogs, current methods to synthesize bicyclic esters and lactones are limited. This limitation is no doubt due to the motif's inherent steric bulk and ring strain, with

substitution increasing the steric difficulties and increasing the number of asymmetric centers. In the wide synthetic substrate scope of DCK derivatives completed since its discovery the bicyclic lactone motif was only added onto the periphery of the molecule using commercially available (S)-(-)-camphanoyl chloride, never synthesized.[27–30] While the availability of this bicyclic reagent is extremely useful, it can only be used to add the bicyclic motif in specific circumstances. The lack of bicyclic synthesis in the DCK-based substrate scope speaks to the difficulty of the component's synthesis, especially given the motif's established biological activity importance and the numerous derivatizations of other motifs.[27–30]

The synthesis of such bicyclic motifs is highly limited in the variety of reagents that can be used. Many of the published procedures are base catalyzed, some using strong bases such as sodium hydroxide.[31,32] While this approach works for simple compounds, the ability to apply it to more complex molecules, especially those with base-sensitive motifs, is a severe hindrance. Other common methods include the use of metal catalysts, whose detriments have already been discussed in Chapter 1,[33,34] or radical initiators.[35] As shown in the DCK studies, camphanoyl chloride can be used to add the motif to a nucleophilic center, but this approach requires an appropriately active atom with minimal steric hindrance to complete. The addition of camphanoyl chloride also does not allow for the integration of the bicyclic motif into the core of the structure. Along with the logistical limitations of many of these common methods, producing compounds with enantioenriched substitution at a non-bridgehead carbon is a difficulty, often producing a mix of diastereomers.[33,35] These restrictions encouraged us to work toward the development of a new, acid-catalyzed synthetic method.

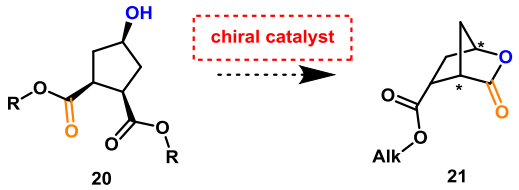


Figure 12. Desymmetrization of Meso Diesters to Enantioenriched Bicycles

The general approach outlined in this thesis for the formation of enantioenriched bicyclic lactones is the desymmetrization of monocyclic, meso diesters (**20**) to bicycles (**21**) through a single step as shown in Figure 12. This transformation includes the use of a chiral phosphoric Brønsted acid catalyst to set all 3 of the asymmetric centers of the resulting bicycle, producing enantioenriched compound **21**. This approach aims to take advantage of the knowledge gained by previous desymmetrization research in the Petersen group with meso diesters and expand the applicability of the methodology.

2.2 Results and Discussion

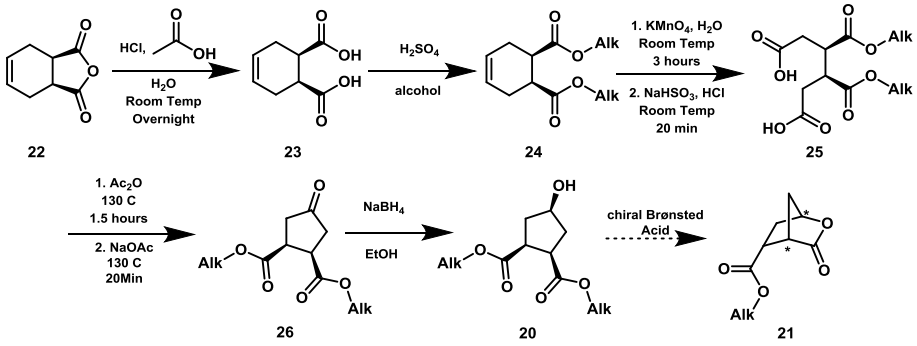


Figure 13. Overall Synthetic Pathway for Enantioenriched Bicyclic Lactones

The overall synthetic scheme for the synthesis of meso cyclopentyl diesters such as **20** and their desymmetrization to bicycle **21** is shown in Figure 13. To begin, the succinic anhydride portion on cyclohexene **22** is opened in acidic conditions, to produce dicarboxylic acid cyclohexene **23**.[36] The dicarboxylic acid then is esterified with a variety

of alcohols in acidic conditions to yield diester **24**.[37] The cyclohexene of the diester is then opened, converting the alkene to a dicarboxylic acid, **25**, with the use of potassium permanganate.[38] Cyclization of **26** into a five-membered cyclic diester lactone **26** is accomplished using acetic anhydride and sodium acetate.[38] This lactone is reduced to an alcohol, **20**, with the use of sodium borohydride before the final chiral Brønsted acid catalyzed cyclization of the compound to enantioenriched bicycle **21**.

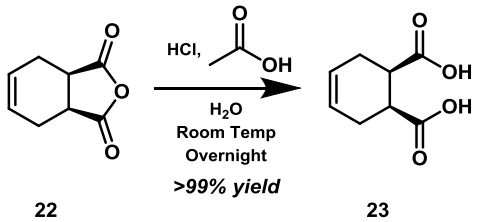


Figure 14. Opening of Succinic Anhydride Ring

The initial synthetic step of opening the succinic anhydride ring of **22** to the dicarboxylic acid **23**, shown in Figure 14, produced >99% desired product.[36] The four diesters (**27**, **28**, **29**, and **30**) were each synthesized utilizing the same general esterification method, shown in Figure 15.[37] The methyl substrate was produced in the highest yield (70%) and the yields decreased as the alkyl group increased in steric bulk and size, with the ethyl, isopropyl, and tert-butyl esters being produced in 55%, 41%, and 20% yields, respectively. Given this yield and steric bulk considerations, the ethyl substrate (**28**) was chosen for further elaboration via the synthetic pathway described above, with the isopropyl substrate (**29**) carried through for comparison.

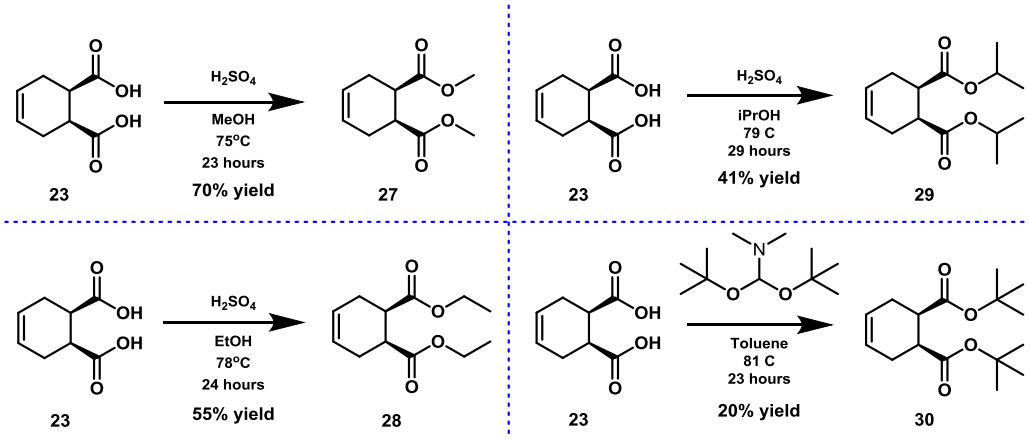


Figure 15. Esterification of Carboxylic Acid Motifs

Cyclohexenes **28** and **29** were treated with potassium permanganate in water, resulting in the formation of dicarboxylic acids, **31** and **32** (Figure 16).[38] Initially this conversion presented some challenges, as the consistency of the reaction solution made the extraction and washes difficult to complete. The addition of a large excess of acid before work up eliminated these difficulties and increased yields from 24% and 20% for the ethyl and isopropyl substrates respectively to >90% yields for both substrates without any purification required.

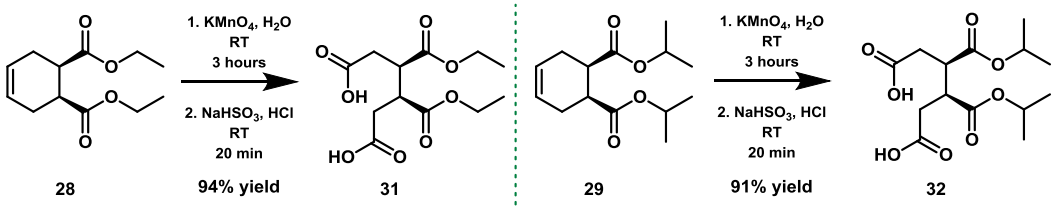


Figure 16. Alkene Cleavage of Diesters

Cyclization of the dicarboxylic acid substrates **31** and **32** was done using sodium acetate and acetic anhydride under reflux to produce **33** and **34** in 54% and 35% yields respectively (Figure 17).[38] This step's yields suffered from the production of reaction byproducts as well as the necessity of purification, being the first synthetic step to require column chromatography. The nontrivial difference between the yield for the ethyl and isopropyl substrates in this step as in previous steps lead us to focus on the more reproducible ethyl compounds in future steps.

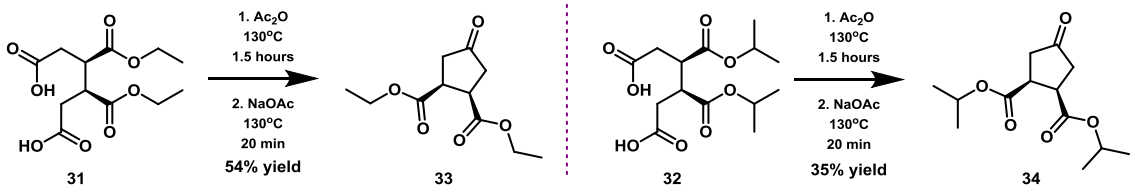


Figure 17. Cyclization of Cleaved Product

Before the key desymmetrization reaction could be attempted, cyclic ketone **33** was reduced to the alcohol **35**, using sodium borohydride in ethanol (Figure 18). As suggested in the representation of compound **35**, the confirmation of the alcohol stereocenter is not known. The steric bulk caused by the cis-diesters would suggest that the hydride would add to the ketone carbon from the opposite side of the molecule, forming the desired all cis diastereomer. The formation of this diastereomer could be confirmed by NOESY 2D NMR, but initially the unidentified major diastereomer was simply collected. This step has yielded product **35** to varying degrees, as seen in Figure 18, with yields ranging from a respectable initial yield of 69%, to yields of 35% and 22% in the most recent two attempts. The difficulty in completing this step with reproducible yields, compounded with the relatively long nature of the synthesis, has caused major setbacks in the ability to make bicyclization attempts. The reason for this yield decrease

has not been determined, as new sodium borohydride, longer reaction times, and higher temperatures have been applied to the reaction, resulting in no major yield improvements. The way in which the reaction is worked up may be one area for improvement, as initially the reaction mixture was simply filtered and dried, while recently a separation of water and organic layers was implemented. This change will be considered in future synthesis, as well as increasing the sodium borohydride equivalences and continuing to alter reaction conditions.

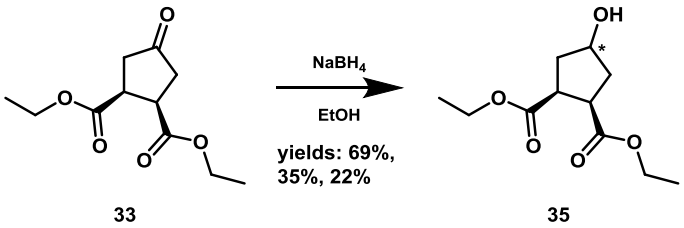


Figure 18. Reduction of Cyclic Ketone

With the starting material synthesized through the described five step pathway, the conversion of meso alcohol **35** to racemic bicycle **36** has been attempted in six combinations of reaction conditions and Brønsted acids (Figure 19). The two acids that have been attempted at this point are *p*-toluenesulfonic acid and camphor sulfonic acid, both of which were chosen because of their similarity of acidic activation to the chiral phosphate catalysts used in the Petersen lab to complete similar cyclizations, as discussed in Chapter 1. Unlike the phosphoric acid catalysts, these Bronsted catalysts do not have the capability to additionally base catalyze the substrate. The increased acidic strength of the compounds used in Figure 19 aims to overcome this activation discrepancy. *p*-Toluenesulfonic acid was used first in three different reaction conditions, most notably changed in temperature and time of reaction, with a variety of products

produced. Recovered starting material was consistently seen as the major result. The final most extreme conditions, reacting **35** with 0.5 equivalents of *p*-toluenesulfonic acid at 100°C, resulted in the addition of the acid into compound **35** at one of the esters and thus other acid catalysts were considered. D-Camphor sulfonic acid was a logical second choice, but once again none of the three different reaction conditions produced desired product **36**, or at least not in large enough quantities to be isolated following column chromatography and identified by NMR.

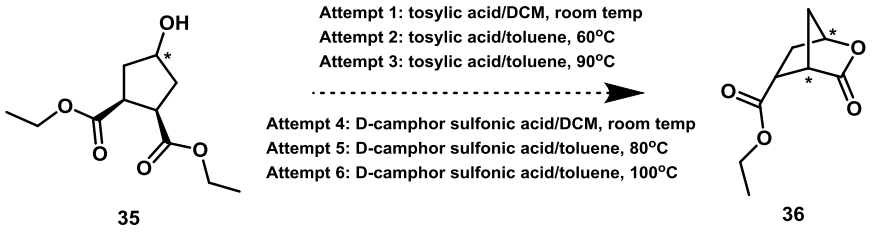


Figure 19. Racemic Cyclization Attempts to Form Bicycle **36**

2.3 Future Work

The difficulties encountered in the synthesis of the current bicyclic targets has spurred the group to further analyze the synthesized starting material and consider new substrates. As mentioned, although the diastereomers of **35** were effectively separated, it is unknown whether the isolated major diastereomer is the necessary all-cis configuration. Due to the cis confirmation of the succinic anhydride in starting material **22** and the lack of synthetic changes to either of the stereocenters in subsequent steps, the diesters of compound **35** are assumed to be cis. If true, the only ambiguity of the overall configuration of compound **35** comes from the reduction of the ketone to the corresponding alcohol. As discussed, there was reasoning to suggest that the formation of the all-cis isomer would be more favorable based on steric bulk from the diesters. As

the all-cis is the diastereomer which could have most readily cyclized, successful production of bicycle **36** would have suggested the isolation of the all-cis diastereomer of compound **35**. The inability to form the bicycle could, therefore, be caused by the isolation and reaction of a trans diastereomer or the actual incapability of the all-cis diasteromer to cyclize. To determine whether compound **35** is the all cis it will be analyzed by 2D NOESY NMR before further cyclization attempts.

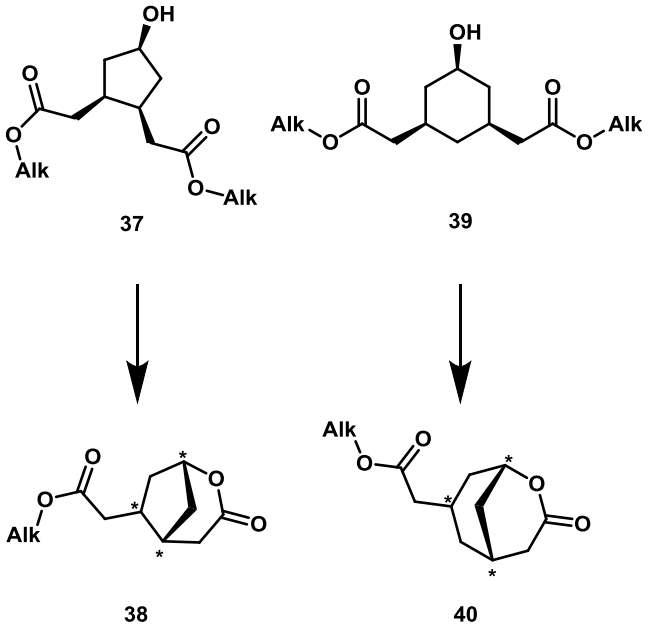


Figure 20. Possible Future Bicyclic Lactone Substrates

Aside from the diastereomer concerns, the ring strain of the bicyclic structure may be a significant obstacle to its formation. In hopes to overcome this more fundamental difficulty, other compounds that may be explored in the future will feature an extension of the ester motifs from the ring. Figure 20 shows two possible new starting material substrates, **37** and **39**, that could potentially produce slightly different bicyclic lactones (**38** and **40**). Both substrates, **37** and **39**, maintain the same basic components

of the starting material, only altered by the inclusion of a carbon between the ring and the diester groups. Hopefully this addition will increase the favorability of the cyclization by both reduce ring strain and provide more free movement of the ester group, potentially allowing it to come closer to the alcohol. Additionally, by extending the ester chains instead of the alcohol moiety the overall achiral, meso nature of the compound remains intact.

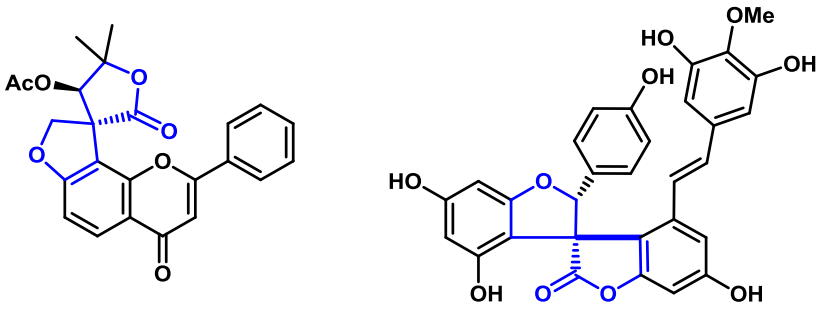
2.4 Conclusion

While the synthesis of the starting material has been completed, the enantioselective synthesis of the target bicyclic lactone substrates remains unaccomplished. The future directions discussed in the previous section are just several ideas for how this project may be adapted and further attempted, with a variety of alkyl chains in the diester as well as Brønsted acid catalysts that could still be explored. With the preliminary results collected, future investigation can be more accurately targeted towards more successful ends.

CHAPTER III

ASYMMETRIC SYNTHESIS OF ENANTIOENRICHED SPIROCYCLES

3.1 Introduction



(+)-glabratephrin (41) **yuccaol C (42)**

Figure 21. Natural Products Glabratephrin and Yuccaol C

The enantioselective synthesis of spirocyclic motifs featuring all carbon centers is both challenging and highly in demand. The difficulty of this process is due to the combined problems of carbon-carbon bond formation and setting an asymmetric center in high enantiomeric excess. Due to these challenges, the demand for synthetic techniques remains, driven by the inclusion of the motif in many complex bioactive molecules. The natural products (+)–glabratephrin (**41**) and yuccaol C (**42**) are two such bioactive compounds (Figure 21). The herb *tephrosia apollinea* is native to Egypt and has produced compounds in a wide variety of natural product families, including rotenoids, isoflavones, flavanols, and flavonoid group, the final group including (+)–glabratephrin.[39,40] This myriad of compounds has shown biological activity in a variety of different ways, but the utility of flavonoids such as (+)–glabratephrin is predominately in

antifungal and antiparasitic applications.[39,40] The synthesis of fully characterized natural compounds such as (+)–glabratephrin could lead to nontraditional synthetic agents, potentially circumventing biological resistance to known compounds and reducing the environmental impact of such crop treatments. Alternatively, the active compounds in *yucca schidigera* have been used in traditional Native American medicine as a complex extract for centuries, providing beneficial therapeutic instead of defensive effects.[41,42] The uses of the bark extract in traditional medicine have been widely varied, but following their identification the active compounds have particularly shown anti-inflammatory and antioxidant properties.[41–44] Yuccaol C is one of several similarly structured compounds found in the yucca extract, the structural family accounting for over half of the active compounds found in the bark.[41]

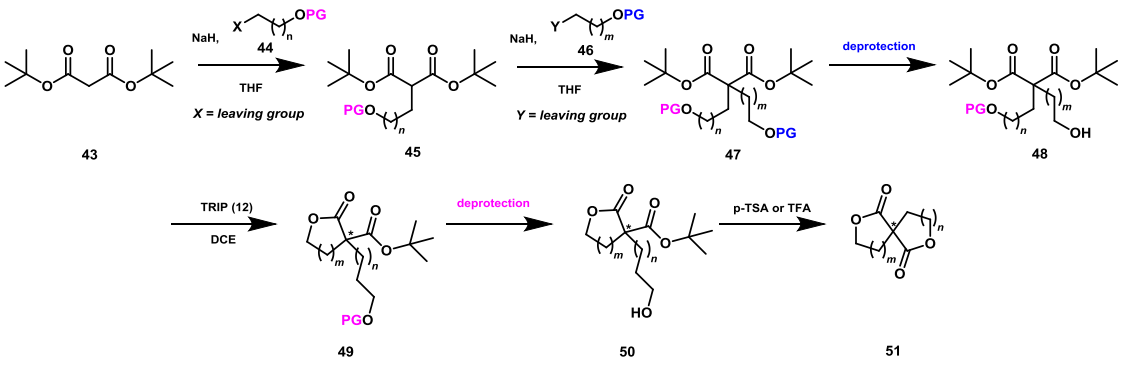


Figure 22. Overall Synthetic Pathway for Spirocycles

An overview of the basic synthesis of the spirocyclic compounds is shown in Figure 22. The starting compound, **43**, is reacted with sodium hydride to form the enolate species, which nucleophilically attacks **44** to undergo a first alkylation. The specific structure of **44** will vary largely based on the substituents and size of the rings desired. The second alkylation from **45** to **47** is carried out in a similar method, using

sodium hydride to remove the remaining acidic hydrogen and initiate the substitution reaction. The removal of the selected protecting group on **47** yields a free alcohol in **48**, which can then be enantioselectively cyclized via a desymmetrization with the chiral Brønsted acid TRIP to **49**. The enantioenriched monocyclic lactone is converted to spirocycle **51** through the deprotection of the second protecting group, exposing the free alcohol in compound **50**, followed by cyclization using an achiral catalyst such as *p*-toluenesulfonic acid or trifluoroacetic acid

The key features of this approach are the use of a chiral phosphoric Brønsted acid catalyst (**12**) with an achiral starting material (**43**) to produce the enantioenriched monocyclic lactone (**49**). The setting the central stereocenter in this step allows for the use of an achiral acid catalyst for the secondary cyclization to **51**. The much lower cost and reaction time of the achiral catalyst makes this approach appealing for multiple reasons. Additionally, while unsubstituted oxygen-containing alkyl chains are shown in Figure 22, the inclusion of nitrogen and substituents have been demonstrated successfully, sparking interest into the range of applicability.

3.2 Previous Work

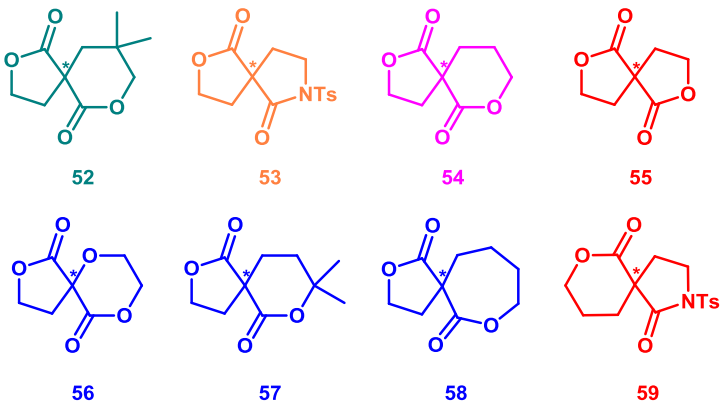


Figure 23. Spirocycles Included in Substrate Scope

The spirocyclic compounds included in the substrate scope of this project at this point are shown in Figure 23. The green compound **52** is the target of the preliminary work directly done and discussed in the following section. The synthesis of the blue compounds (**56**, **57**, and **58**) is in progress and is being worked on by other members of the Petersen lab, while the red, pink, and orange compounds (**53**, **54**, **55**, and **56**) have been synthesized and characterized by Jennifer Wilent of the Petersen group. The orange compound, **53**, is currently being resynthesized and recrystallized to obtain higher enantiopurity and crystals suitable for x-ray crystallography analysis. Compound **54** in pink is the focus of a targeted synthesis to study the reaction pathway.

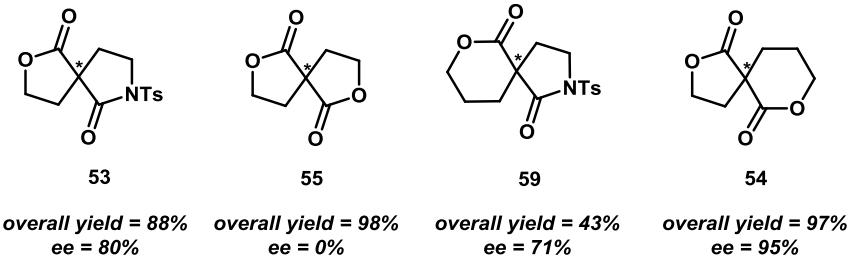


Figure 24. Results for Completed Spirocyclic Compounds

The preliminary spirocyclic work done by other members of the Petersen group has been extensive. Four compounds have been completed and two others have been started by Jennifer Wilent, the individual who initiated the project. The structures, percent yields, and enantiomeric excess of the completed compounds is provided in Figure 24. The completed substrates are the basis of this product. The spirocyclic γ,γ-bislactone **55** does not contain a traditional asymmetric center, but instead possesses axial chirality (Figure 25). Due to this absence of a traditional asymmetric center, which would contain four different groups, the precyclized starting material contains two enantiotopic groups, making the ability of the chiral Brønsted acid to cyclize

enantioselectively much more difficult. This lack of selectivity is the reason for the 0% enantiomeric excess.

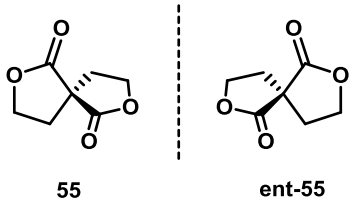


Figure 25. Depiction of Axial Chirality in Compound **55**

Compounds **53**, **56**, **57** and **58**, shown in Figure 23, are currently being worked on in the lab. Compound 39 was completed by Jennifer Wilent, but is now being resynthesized as part of this project to improve the reported 80% enantiomeric excess by recrystallation. Amber Kelly is exploring the synthesis of **56** and continuing the synthesis of **57** begun by Jennifer Wilent with the assistance of Nick Chambers. The production of **58** has been started by Eni Minerali. The synthesis of the completed and unfinished compounds follows the same general synthesis pathway shown in Figure 22.

3.3 Results and Discussion

3.3.1 Novel Substrate Synthesis

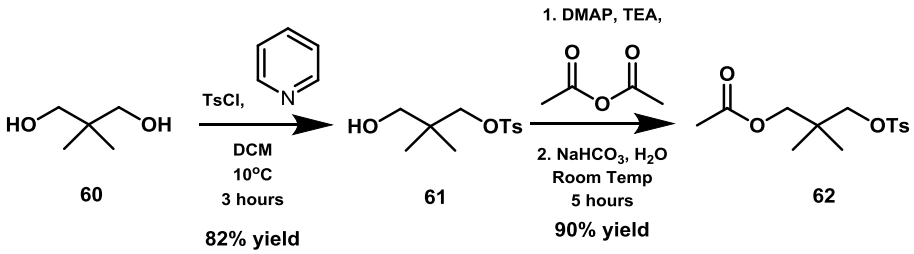


Figure 26. Synthesis of Alkylating Agent **62**

For spirocycle **52** a synthesis starting with **60** was required to produce alkylating agent **62**, shown in Figure 26.[45,46] First one of the alcohols of the diol **60** was converted to a tosyl group through a reaction with tosyl chloride and pyridine to produce **61**.[45] Next, the other alcohol was protected with an acetyl group when **61** was reacted with acetic anhydride and 4-dimethylaminopyridine to yield **62**.[46] Both conversions were completed in good yields, 82% and 90% respectively, although the tosylation required column separation to remove remaining starting material from the product.

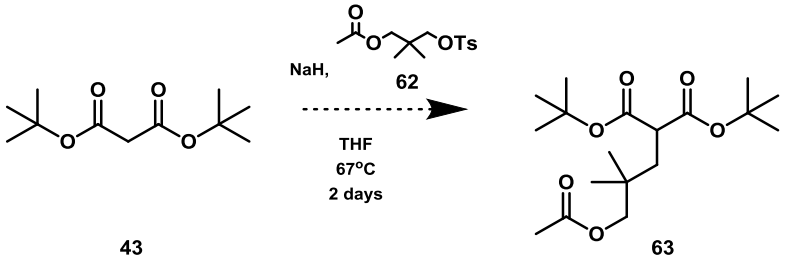


Figure 27. Attempted Alkylation using Compound **62**

With **62** synthesized, the previously described first alkylation to produce compound **63** was attempted (Figure 27). The position of the dimethyl carbon in compound **62** makes the substitution reaction more difficult, as an S_N2 reaction is being attempted on a neopentyllic carbon. Initial attempts to perform this substitution have been unsuccessful with the tosylated compound **62**, so an even better leaving group will be used to overcome the higher steric barrier. A mesylate group will be the first new leaving group tested, but iodide may be used if the mesylate compound is still unsuccessful. Both leaving groups have been used successfully in similar nucleophilic attacks of malonate compounds, **64** and **66** in Figure 28, at neopentyl carbons to form alkylated malonates, **65** and **67**, in good yields.[47,48]

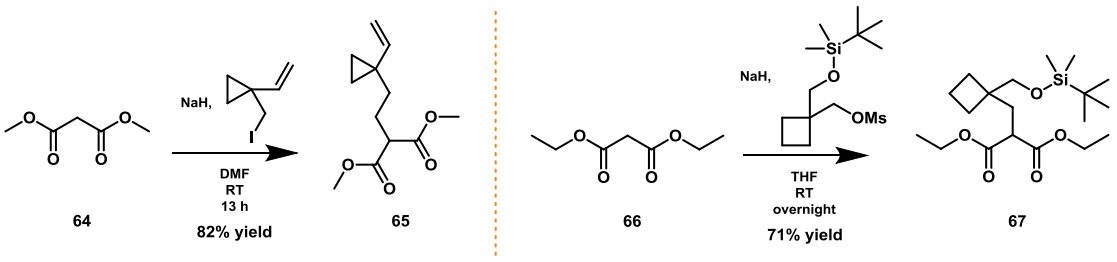


Figure 28. Literature Examples of Alkylation at a Neopentyl Carbon

With this precedent in mind, the synthesis of the alkylating agent for the synthesis of spirocycle **52** was altered. The initial change was the replacement of the tosyl leaving group on compound **62** with a mesyl, a less sterically hindering and more readily removed group. To synthesize this mesyl derivative diol **60** was again mixed with pyridine in dichloromethane, but this time with methanesulfonyl chloride and at 0^{o}C (Figure 29). The reaction proceeded successfully, producing the mesylated compound **68**, but extremely close R_f values between the desired product and side products made purification extremely difficult and so an accurate yield could not be determined. The somewhat purified product was further reacted with 4-dimethylaminopyridine, acetic anhydride, and triethylamine to protect the remaining alcohol group of **68** to yield compound **69** as shown in Figure 29. This transformation once again produced many side products which made purification by column chromatography necessary, but thankfully the R_f difficulties of the previous synthesis did not persist. The addition of 0.1% triethylamine to the chromatography solvent system helped to prevent the removal of the mesylate group by ensuring a nonacidic environment. Following purification, the desired product **69** was collected in an overall 37% yield.

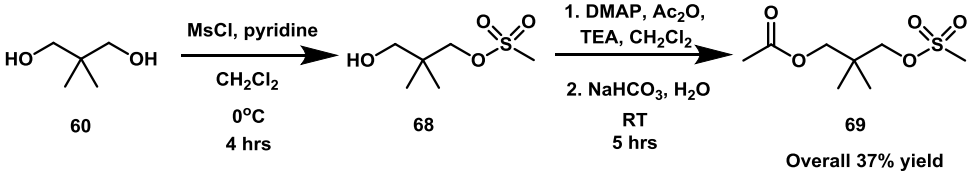


Figure 29. Initial Synthetic Pathway for Compound **69**

To increase the overall yield for the synthesis of the alkylating agent **69**, eliminate the purification difficulties encountered during the synthesis of compound **68**, and reduce the number of steps in which the mesyl group needed to stay attached, the order of the alcohol group modifications was switched (Figure 30). To produce acetylated compound **70** from diol **60** the latter was reacted with 4-dimethylaminopyridine, acetic anhydride, and triethylamine similarly to previous acetylations, but with the equivalence of acetic anhydride reduced from 1.7 to 1 to discourage diacetylation. The reaction successfully produced the monoacetylated product **70** in 51% yield without separation difficulty. The mesyl group was then added to compound **70** using methanesulfonyl chloride and pyridine, now being able to use an excess of the mesylate reagent, but the production of side products and decreased the yield of the desired product.

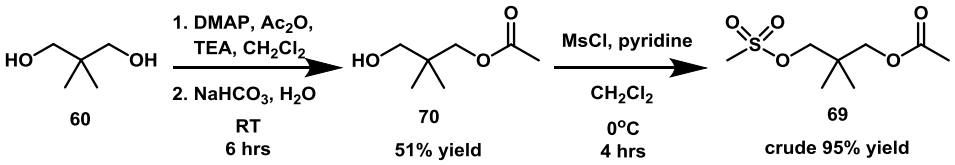
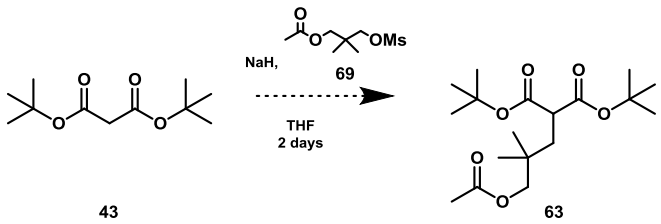


Figure 30. Alternative Synthetic Pathway for Compound **69**

Attempts to use compound **69** in an alkylation reaction with di-tert-butyl malonate to yield compound **63** were carried out with the same reagents but in differing reaction

environments and equivalences. The conditions and equivalences for these attempts are detailed in Table 1.

Table 1. Reaction Conditions for Alkylation Attempts using Compound **69**



43 63

Malonate equivalence	NaH equivalence	Alkylating agent equivalence	Temperature conditions
1	1.5	1	Reflux
1	0.67	0.50	Room temperature

The first attempt mimicked the reaction conditions of alkylations performed previously in the Petersen group. The alternate reaction conditions were based off a similar neopentyl alkylation done by Liu et. al. and decreased the equivalences of all reagents and the temperature of reaction to room temperature rather than under reflux. Test reactions for these two sets of conditions were carried out simultaneously on small scale. Unfortunately, neither of these conditions yielded the desired product **63** in significant quantities.

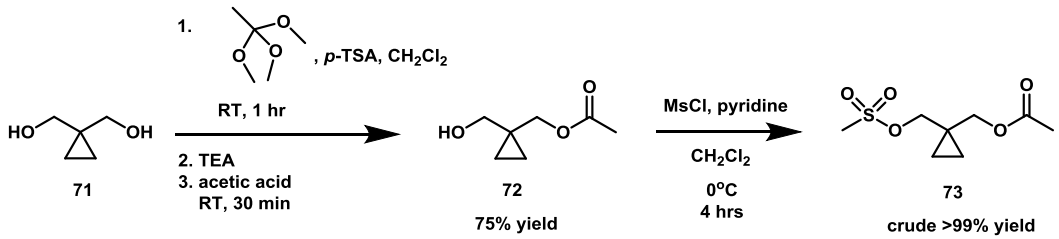


Figure 31. Synthesis of Compound **73**

Due to the literature precedent of S_N2 reactions occurring at centers neopentyl to a cyclopropane connecting carbon,[48] investigation into the cyclopropane diol **71** commenced. Much of the work to produce the alkylating agent **73** was run directly following the dimethyl substrate **69**, and so the reactions and their order were nearly identical (Figure 31). The one major deviation from the dimethyl synthetic route was the discovery of an alternative acetylation procedure which could yield monoacetylated **72** in yields higher than 50% in a fraction of the time with very simplistic purification.[49] This method was eventually applied to both substrates, giving a yield of 75% and 68% for the cyclopropyl and dimethyl diols respectively (Figure 31, 32). While this procedure improved the yield of the acetylation, the starting diol's much higher cost has been a major synthetic constraint. Due to this, reactions were run on small scale, causing difficulties when side products were produced in the following mesylation step. The small scale, in addition to concerns of mesylate removal during column purification, resulted in the use of a crude mixture of **73** for the alkylation attempts. These attempts have yet to produce desired product in significant yields.

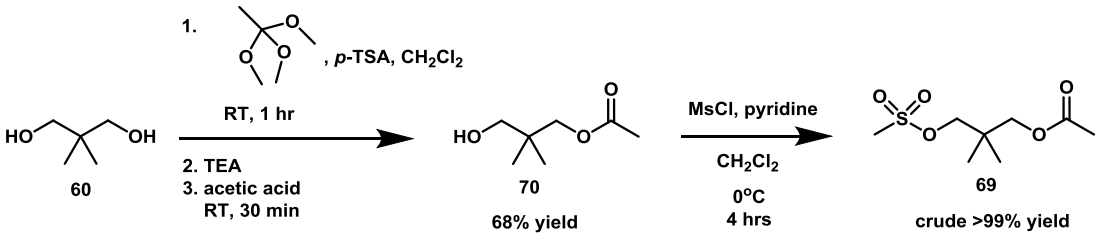


Figure 32. Incorporation of Alternative Acetylation into Synthesis of Compound **69**

3.3.2 Synthesis and Recrystallization of Compound 53

As shown in Figure 24, compound **53** was previously synthesized in 88% yield and 80% enantiomeric excess. While this enantioselectivity is good, we proposed the use of recrystallization to improve the enantiopurity and thus resynthesis of the substrate was required. The interest in obtaining a high enantiomeric excess for compound **53** is partially due to its lactone-lactam construction. Producing a lactone-lactam in similar enantiopurity to the lactone-lactone substrates would strengthen the applicability of the method to other core functional groups. Thus, compound **53** was resynthesized in efforts to produce a large quantity of material on which to attempt recrystallization to improve the compound's enantiomeric excess.

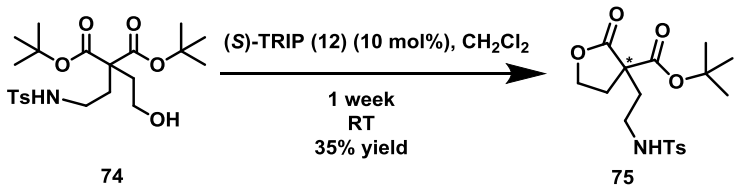


Figure 33. Enantioselective Cyclization of Compound **75**

The initial steps to resynthesizing **53** were started by Dr. Jennifer Wilent before her exit from the group. The work up of the first cyclization to compound **75** was the initial step following her involvement, and the yield from this step was only 35**%** (Figure 33). This monocyclic product **75** was cyclized to spirocycle **53** as shown in Figure 34, but the small yield of the previous cyclization deemed a full additional synthesis necessary.

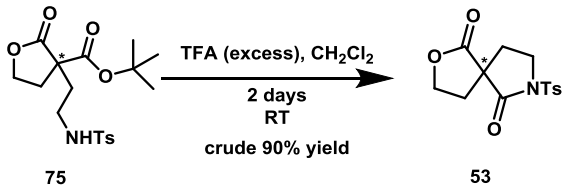


Figure 34. Cyclization of Compound **75**

The first steps of the synthesis (Figure 35) involve the dialkylation of **43** to **76**, each alkylation using sodium hydride as the base to form the necessary enolate. The benzyl ether was added to the di-*tert*-butyl malonate in 72% yield, followed by the addition of *N*-tosylaziridine to produce compound **76** in 51% yield.

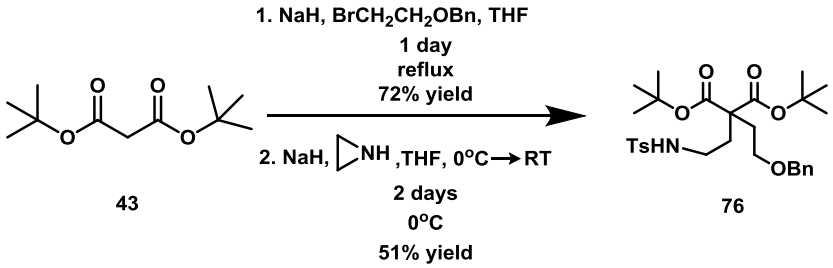


Figure 35. Alkylation Steps to Form Compound **76**

The deprotection of the benzyl group from the oxygen was then completed by hydrogenolysis yielding compound **74**, which was then be cyclized enantioselectively using TRIP catalyst to **75** (Figure 36). Unfortunately, the attempt to perform the second cyclization was slowed by contamination of the catalyst that lowered its reactivity. This was only realized after TLC analysis of the reaction progress and consultation with other group members. Due to this, the reaction was run for over 3 weeks and a second addition of the catalyst was added. The purification and yield determination for this cyclization are forthcoming.

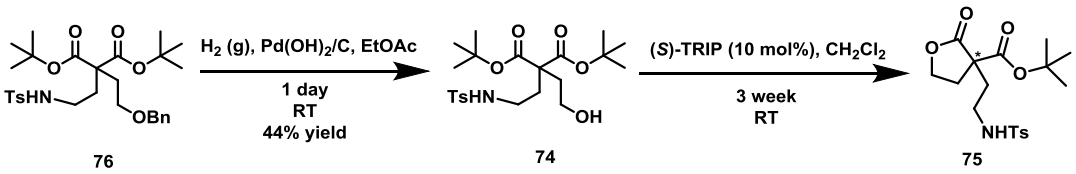


Figure 36. Deprotection and Cyclization to Yield Compound **75**

3.3.3 Reaction Pathway Study Synthesis

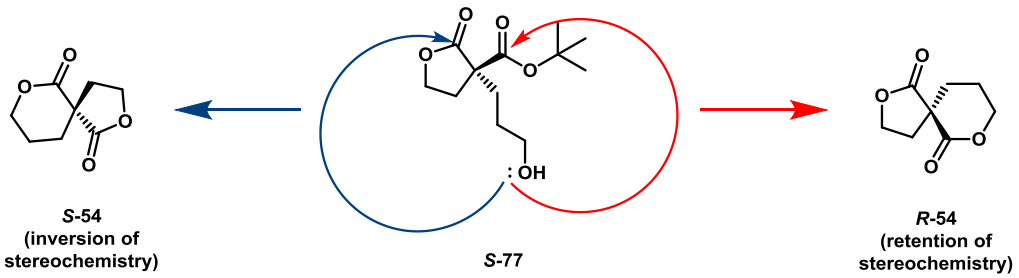


Figure 37. Potential Pathways for Secondary Cyclization

While the basic structure of the monocyclic and spirocyclic products can be determined through NMR and mass spectrometry, the absolute configuration of the two compounds cannot be derived from these two achiral analytical methods. For the configuration of the stereocenter to be determined, a chiral solvent can be used for NMR analysis, or a crystal structure of each of the compounds would be needed. Due to this lack of information, the pathway of second cyclization has yet to be determined. Figure 37 shows the two potential cyclization routes from monocyclic **77** to spirocyclic **54**. The first pathway, shown in red, features the attack of the tert-butyl ester by the free alcohol, resulting in the loss of tert-butoxide and the retention of stereochemistry at the central asymmetric center. Alternatively, the blue arrows show the attack of the lactone carbonyl by the alcohol, which would cause the subsequent opening and recyclization of the 5-membered ring, inverting the stereochemistry of **54**.

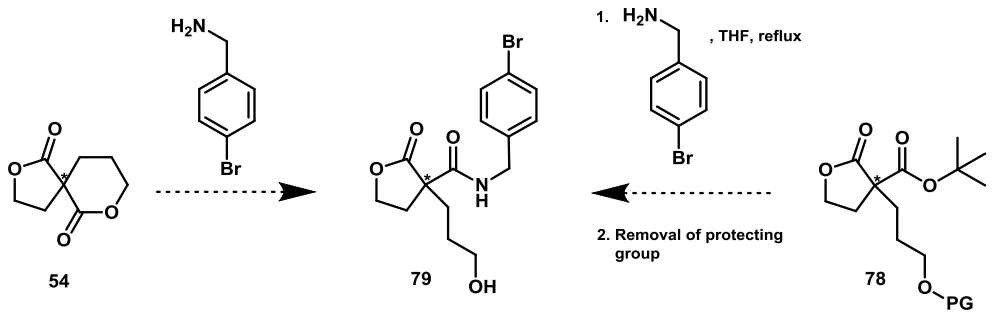


Figure 38. Planned Conversions to Compound **79**

To determine which of the previously discussed pathways accounts for the conformation of bicycle **54**, compound **79** will be synthesized from **54** and **78** as shown in Figure 38. Compound **79** will be synthesized from the spirocyclic compound **54** via the attack of 4-bromobenzylamine at the carbonyl of the 6-membered lactone, resulting in the opening of the ring and formation of the amide in the product. The conversion of monocyclic **78** to compound **79** will use similar methods, but instead using the amine to attack at the ester position.[50] The final step will be the removal of the protecting group on the alcohol, yielding **79**. Attempts to crystallize the supply of **79** produced from each method will be made to determine the absolute configuration. The rotation of both compounds will also be measured using the polarimeter and compared. If the rotation of compound **79** produced from spirocycle **54** matches the rotation of the same compound synthesized from compound **78**, the attack of the free alcohol at the lactone will be supported pathway. The opposite rotation will suggest the attack at the tert-butyl ester is the dominant pathway.

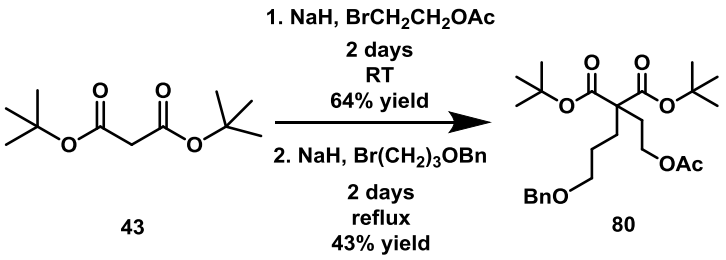


Figure 39. Initial Alkylation Reaction Sequence for Synthesis of Compound **80**

The use of directed synthesis to study the reaction pathway first requires the synthesis of the monocyclic and spirocyclic compounds. As shown in Figure 39, the first transformation uses sodium hydride to complete 2 alkylations, yielding product **80** after two steps. Previous syntheses done in the Petersen lab had done these in the order shown in Figure 39, with the larger benzylated alkylation agent added second. While this was successful in the past, current attempts to complete this synthesis required heat in the addition of this second alkylating agent and this caused the removal of the acetyl protecting group and the racemic cyclization to compound **78**. To discourage this, the heat was lowered to room temperature and 40^{o}C, but many side products and minimal desired product were produced in both cases. In hopes to alleviate these problems the order of the alkylating agents was reversed, now using the benzylated compound in the first step Figure 40). While there were separation difficulties between the monoalkylated intermediate and the benzyl alkylating agent, most of the benzyl alkylating agent is removed by the time the second alkylation is finished, allowing for easier separation.

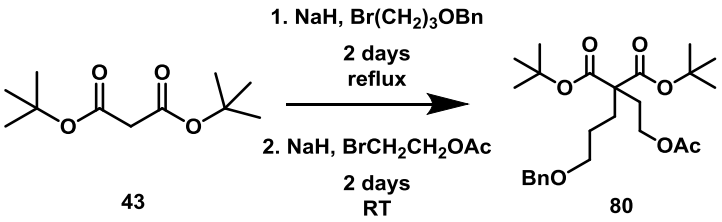


Figure 40. Alternative Alkylation Sequence to Yield Compound **80**

Following the production of **80** the acetyl protecting group was removed using potassium carbonate to yield **81**. The alcohol was then cyclized using TRIP (**12**) catalyst to yield **77**, as shown in Figure 41. Due to the difficulties of the alkylating sequence the monocyclic product has only been isolated is minor yields, but with the sequence effects now resolved this should be improved upon.

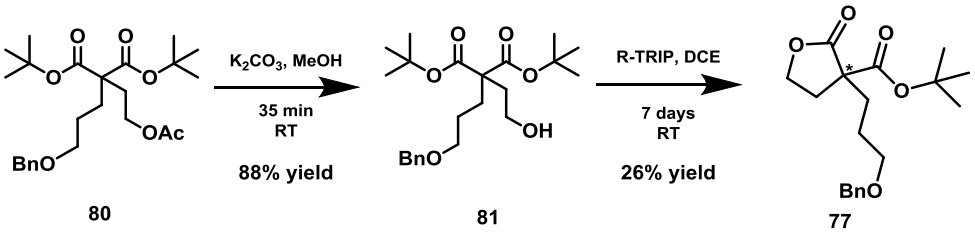


Figure 41. Deprotection and Cyclization to Yield Compound **77**

3.4 Future Work

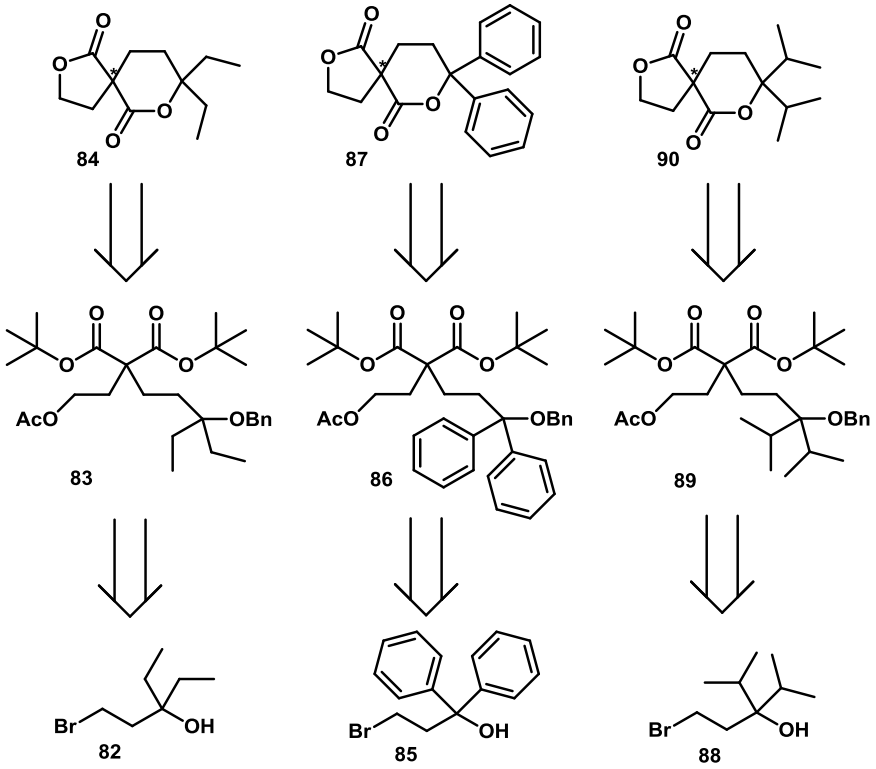


Figure 42. Potential Future Spirocyclic Substrates

While difficulties have been encountered in the synthesis of the attempted alkylating agent and spirocyclic substrate, investigation into several new alkylating agents has already begun. The iodide leaving group is still an unexplored avenue for the successful production of compound **52**, but its incorporation can be even more problematic than that of the mesylate. Due to this remaining difficulty, alternative substrates **84**-**90** shown in Figure 42 are being considered. Alkylation to obtain these new compounds would no longer involve performing an S_N2 reaction at a neopentyl carbon, presumably the main source of synthetic difficulty. The compounds **84**-**90** are an expansion of the substitution in compound **57**, instead including more sterically hindered

substituent groups. While the bulkiness of these groups may make the cyclization of the alcohol to the lactone too sterically hindered, cyclization could alternatively be aided by the bulk of the groups in Thorpe-Ingold effect and occur more easily.[51] The potential angle compression caused by the bulky groups germinal to the alcohol group could position the alcohol even closer to the electrophilic carbonyl carbon, helping to overcome the steric barrier of the cyclization.[51]

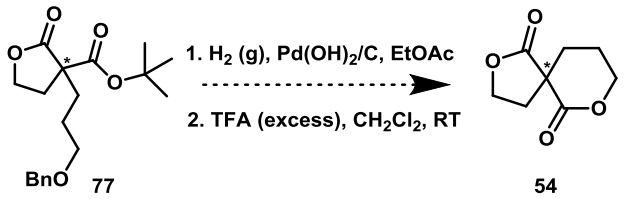


Figure 43. Planned Deprotection and Cyclization of Compound **77**

The targeted synthesis of compound **54** is another area which needs further development. The alternate alkylation sequence appears to produce desired product in higher yields while eliminating premature cyclization. This approach will be scaled up now that its benefits have been established, leading to a substantial increase in lactone products for further reaction. The monocyclic **77** will be converted to the spirocycle **54** through a deprotection and achiral cyclization as detailed in Figure 43. The modification of compounds **54** and **77** to compound **79** will be done as detailed in Figure 38. Alternatively, the idea of reaction monitoring through NMR has been suggested and may provide more immediate insight into the reaction pathway. If the secondary cyclization reaction is slow enough to be monitored by NMR, the differences in ^{1}H NMR should indicate the reaction pathway. The sets of vicinal hydrogens to the two nucleophilic oxygens have distinct peaks from one another, in addition to the shift difference between the cyclized and uncyclized forms of each. Using this information, it should be clear

whether the cyclized vicinal hydrogens are being altered by ring opening. This approach has yet to be attempted and highly depends on the reaction rate for the second cyclization, but if applicable it would eliminate the need for lengthy synthesis while providing the same insight.

3.5 Conclusion

This chapter has shown the progress made towards the completion of a more extensive spirocyclic substrate scope and the targeted synthesis to understand the mechanism pathway. Continued work on these targets is already underway, including the preliminary synthesis of new alkylating agents. Despite some synthetic issues, both in the synthesis of compounds produced previously in the group and novel substrates, the overall desymmetrization strategy remains effective.

CHAPTER IV

EXPERIMENTAL

4.1 General Information

Unless otherwise noted, all reagents and solvents were acquired from commercial sources and used without additional purification. Anhydrous solvents were dried via standard procedures. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained through use of a 400 MHz or 500 MHz spectrometer using chloroform-*d* or acetone-d_6 at room temperature. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^{1}H NMR splitting patterns: s = singlet, d = doublet, m = multiplet, t = triplet, q = quartet, quint = quintet, sept = septet. All reactions were monitored via thin layer chromatography (TLC) using silica G F_{254} precoated glass-backed plates. Flash column chromatography was done using flash grade silica gel (particle size: 40-63 µm, 230 x 400 mesh).

4.2 Synthesis of Compound 23

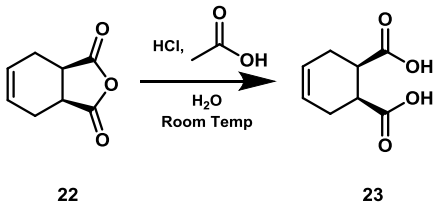


Figure 44. Synthesis of Compound **23**

To a solution of crushed *cis*-1,2,3,6-tetrahydrophthalic anhydride pellets (1.00 g, 6.57 mmol) in acetic acid (1.85 mL, 6.57 mmol) was added 10 drops of 1 M hydrochloric

acid dropwise, followed by an aliquot of water (9.27 mL). The reaction solution was stirred overnight after which time, the solvent was removed through rotary-evaporation to yield the pure product **23** as a white, powdery solid (1.11g, >99% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 5.62 (s, 2H), 3.00 (m, 2H), 2.54 (dd, J = 16.3, 5.3 Hz, 2H), 2.33 (dd, J = 16.4, 5.5 Hz, 2H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 174.0, 125.3, 38.9, 25.9.

4.3 Synthesis of Compounds 27-29

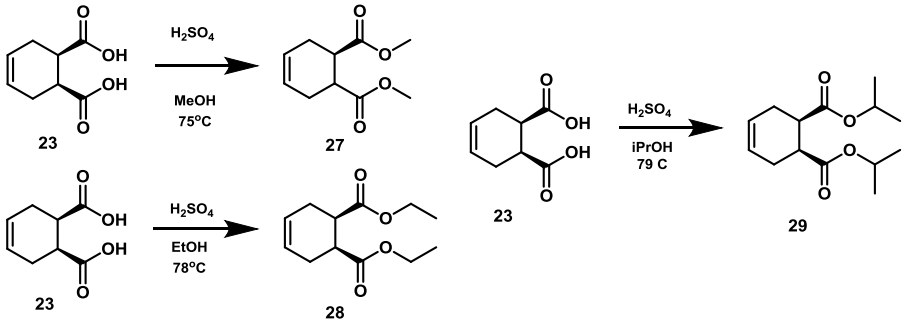


Figure 45. Synthesis of Compounds **27**-**29**

To a flame dried 25 mL round bottom flask under Argon was added (±)-*cis*-4-cyclohexene-1,2-dicarboxylic acid **23** (0.552 g, 3.24 mmol) and methanol (dry, 7.90 mL). An aliquot of concentrated sulfuric acid (5 M, 0.143 mL, 0.713 mmol) was added dropwise to the reaction solution before the flask was heated to 75°C with an oil bath. The flask was removed from the oil bath after overnight reaction and the solvent was removed using rotary-evaporation. Once most of the solvent was removed, the residue was transferred to a separatory funnel and rinsed with ethyl acetate (10 mL). The solution was washed with a saturated sodium bicarbonate solution (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x10mL). The combined organic layers were washed with a saturated sodium chloride solution (20 mL) and dried with magnesium sulfate. The mixture was filtered and the resulting solution was condensed

using rotary-evaporation. The concentrated residue was purified using flash chromatography on silica gel (2% methanol in CH_2Cl_2) to yield dimethyl ester product **27** as an oil (0.4531 g, 71% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.63 (d, *J* = 3.0 Hz, 2H), 3.65 (s, 6H), 3.01 (t, *J* = 5.3 Hz, 2H), 2.51 (dd, *J* = 15.6, 4.4 Hz, 2H), 2.31 (dd, *J* = 15.4, 4.4 Hz, 2H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 173.12, 125.07, 51.01, 39.29, 25.61.

Diethyl product (**28**): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.65 (s, 2H), 4.12 (qt, *J* = 7.1, 3.4 Hz, 4H), 3.01 (t, *J* = 5.7 Hz, 2H), 2.52 (dd, *J* = 16.6, 6.0 Hz, 2H), 2.32 (dd, *J* = 16.4, 6.1 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.4, 125.3, 60.7, 39.9, 25.8, 14.2.

Diisopropyl product (**29**): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.65 (s, 2H), 5.00 (sept, *J* = 6.3 Hz, 2H), 2.97 (t, *J* = 5.3 Hz, 2H), 2.51 (dd, *J* = 16.5, 5.5 Hz, 2H), 2.30 (dd, *J* = 16.5, 5.2 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 12H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.9, 125.3, 68.0, 39.9, 25.9, 21.9.

4.4 Synthesis of Compound 30

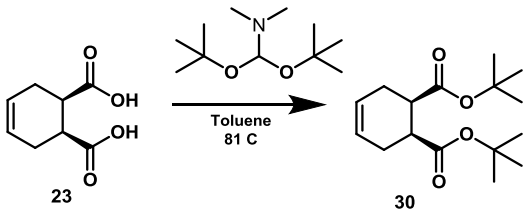


Figure 46. Synthesis of Compound **30**

A solution of (±)-*cis*-4-cyclohexene-1,2-dicarboxylic acid **23** (0.250 g, 1.47 mmol) in toluene (3.75 mL) was made in an oven-dried two-necked 25 mL round bottom flask under inert atmosphere. The flask was heated to 80^{o}C with an oil bath and heated for 10

minutes before *N*,*N*-dimethylformamide di-*tert*-butyl acetal (1.80 g, 8.85 mmol) was added. The reaction flask was removed from the oil bath after 43 hours and transferred to a separatory funnel with ethyl acetate (10 mL). The reaction solution was washed with deionized water (20 mL), then the organic phase was washed with a saturated sodium bicarbonate solution (20 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and concentrated by rotary-evaporation. The condensed residue was purified using flash chromatography on silica gel (10→15% diethyl ether in hexanes) to yield ditertbutyl product **30** (0.0875 g, 21% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 5.59 (t, *J* = 1.5 Hz, 2H), 2.85 (td, *J* = 6.4, 5.6, 2.0 Hz, 2H), 2.46 (ddd, *J* = 15.9, 6.5, 2.1 Hz, 2H), 2.24 (ddd, *J* = 16.0, 6.5, 1.8 Hz, 2H), 1.39 (s, 18H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 172.1, 125.2, 79.6, 40.2, 27.4, 26.0.

4.5 Synthesis of Compounds 31-32

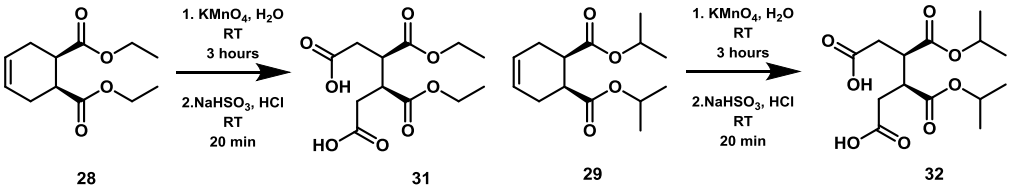


Figure 47. Synthesis of Compounds **31**-**32**

A solution of potassium permanganate (2.86 g, 18.1 mmol) in deionized water (13.90 mL) was made in a 50 mL round bottom flask and stirred at room temperature open to air for 1 hour. The flask was cooled to 2°C with an ice water bath before diester product **28** (1.296 g, 5.729 mmol) dissolved in acetone (3 mL) was added slowly to the solution. The reaction flask was removed from the ice bath once the addition was

completed and was left to stir at room temperature. After 3 hours of reaction, 3 M hydrochloric acid solution were slowly added to the flask until the reaction solution changed from viscous, dark purple to a clear liquid. The solution was transferred to a separatory funnel and extracted using 1:1 ethyl acetate/THF (15 mL). The aqueous layer was extracted with 1:1 ethyl acetate/THF (3 x 10 mL) and the combined organic layers were washed with saturated sodium chloride solution (20 mL), dried over magnesium sulfate, filtered, and condensed by rotary evaporation to yield ring opened product **31** as a white solid (1.570 g, 94% yield).

Ethyl ester (**31**): ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.09 (qq, J = 10.6, 7.0 Hz, 4H), 3.06 (m, 2H), 2.71 (dd, J = 17.3, 10.0 Hz, 1H), 2.51 (dd, J = 17.2, 3.9 Hz, 2H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 172.1, 172.0, 60.6, 42.3, 32.3, 13.6.

Isopropyl ester (**32**): ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.94 (sept, J = 6.3 Hz, 2H), 3.23 (m, 2H), 2.71 (dd, J = 17.0, 10.1 Hz, 2H), 2.48 (m, 2H), 1.20 (d, J = 3.7 Hz, 6H), 1.18 (d, J = 3.9 Hz, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 172.17, 171.5, 68.1, 42.3, 32.3, 21.1.

4.6 Synthesis of Compounds 33-34

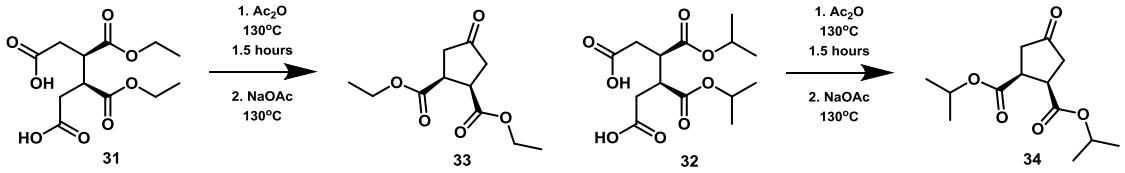


Figure 48. Synthesis of Compounds **33**-**34**

A solution of ring opened product **31** (1.36 g, 4.70 mmol) in acetic anhydride (6.82 mL) was prepared in a flame-dried 25 mL two-necked round bottom flask under inert atmosphere. The reaction flask was heated to 130°C with a oil bath and stirred for 1.5 hours. Acetic acid sodium salt (0.341 g, 4.153 mmol) was then added and the

mixture was stirred for several additional minutes before the flask was removed from the oil bath. Once the flask had cooled to room temperature it was cooled to 2°C in an ice bath and methanol (1 mL) was slowly added, followed by deionized water (2 mL). Sodium bicarbonate (0.454 g, 5.403 mmol) was added to the reaction solution after several minutes of stirring, resulting in bubbling of the solution. Once the bubbling had ceased, the solution was transferred to a separatory funnel and and extracted with dichloromethane (10 mL). The aqueous layer was washed with dichloromethane (2 x 10 mL) , the organic layers were combined, and the combined layers were washed with saturated sodium chloride solution (20 mL). The resulting organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The residue was purified using flash chromatography on silica gel (50→60% diethyl ether in hexanes) to yield ketone cyclized product **33** as an oil (0.5572 g, 52% yield).

Ethyl ester (**33**): ^{1}H NMR (400 MHz, Acetone-d6) δ 4.08 (q, *J* = 7.2 Hz, 4H), 3.53 (m, 2H), 2.50 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 212.7, 172.4, 60.5, 43.2, 40.0, 13.6.

Isopropyl ester (**34**): 1H NMR (400 MHz, Acetone-d6) δ 4.92 (sept, *J* = 6.4 Hz, 2H), 3.46 (m, 2H), 2.48 (m, 4H), 1.19 (d, *J* = 2.0 Hz, 6H), 1.18 (d, *J* = 2.2 Hz, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 212.8, 171.8, 68.0, 43.3, 40.2, 21.1.

4.7 Synthesis of Compound 35

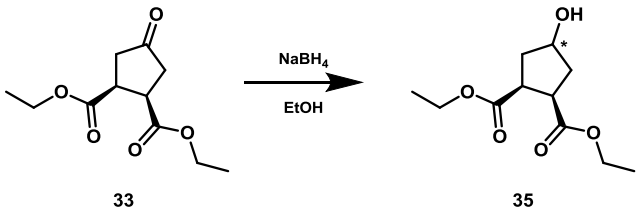


Figure 49. Synthesis of Compound **35**

A solution of cyclized ketone product **33** (0.555 g, 2.431 mmol) in ethanol (29.9 mL) was made in a flame-dried 10 mL round bottom flask and put under inert atmosphere. The solution was cooled to 5°C with an ice water bath and stirred for several minutes before sodium borohydride (0.109 g, 2.893 mmol) was added. After stirring the reaction solution for an hour in the ice water bath, saturated sodium chloride solution (15 mL) was added to the round bottom flask and the solution was stirred for several minutes. The reaction solution was filtered to remove sodium chloride precipitate and the filtered solution was dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The condensed residue was purified by flash column chromatography on silica gel (50→100% diethyl ether in hexanes) yielding alcohol product **35** (0.382 g, 69% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.21 (q, J = 6.6 Hz, 1H), 4.03 (q, J = 7.2 Hz, 4H), 3.02 (td, J = 5.7, 2.9 Hz, 2H), 2.20 (m, 2H), 1.89 (m, 2H), 1.16 (t, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 173.4, 71.2, 60.0, 44.4, 38.0, 13.7.

4.8 Synthesis of Compound 62

4.8.1 Tosylated Intermediate 61

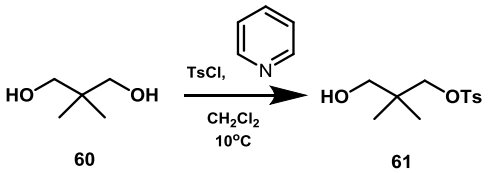


Figure 50. Tosylation to Intermediate **61**

To a flame-dried 10 mL round bottom flask was added 2,2-dimethyl-1,3-propanediol (**60**) (0.200 g, 1.920 mmol), pyridine (0.110 mL, 1.36 mmol), and dichloromethane (0.645 mL). The solution was stirred for several minutes at room temperature before the flask was cooled with a 10°C ice water bath. An additional flame-dried 10 mL round bottom flask under inert atmosphere was charged with 4-toluenesulfonyl chloride (0.074 g, 0.386 mmol) and dichloromethane (0.386 mL). The flask containing dimethyl diol was removed from the ice water bath and replaced with the second flask before the diol solution was transferred slowly via syringe to the 4-toluenesulfonyl chloride solution. The resulting reaction solution was stirred in the ice water bath. After 3 hours, the flask was removed and an aliquot of ethyl acetate (5 mL) was added to the reaction solution and stirred before the solution was transferred to a separatory funnel. Additional ethyl acetate was added (5 mL) and the reaction solution was washed with saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL), the organic layers were combined, washed with saturated sodium chloride solution (20 mL), dried over magnesium sulfate, filtered, and finally condensed through rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (20→40% ethyl acetate in hexanes) to

yield tosylated product **61** as an oil (0.0832 g, 88% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.77 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 3.81 (s, 2H), 3.26 (d, J = 4.0 Hz, 2H), 2.89 (s, 1H), 2.42 (s, 3H), 0.81 (s, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 144.9, 133.4, 130.0, 127.9, 75.6, 67.0, 36.3, 20.7, 20.5.

4.8.2 Compound 62

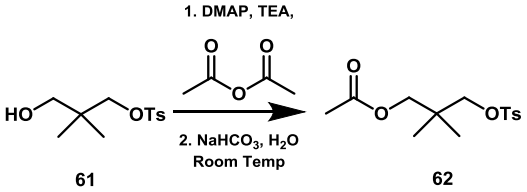


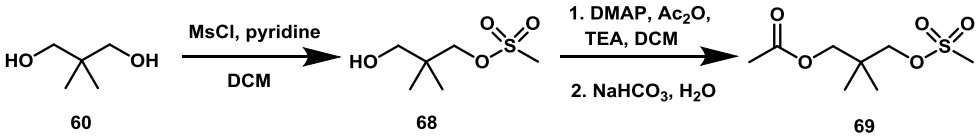
Figure 51. Acetylation to Compound **62**

A solution of tosylated product **61** (0.0939 g, 0.363 mmol) in dichloromethane (2.42 mL) was made in a flame-dried 10 mL round bottom flask under inert atmosphere. After stirring for several minutes at room temperature, 4-dimethylaminopyridine (0.0021 g, 0.0174 mmol), triethylamine (0.051 mL, 0.367 mmol), and acetic anhydride (0.058 mL, 0.617 mmol) were added to the reaction flask and the solution was stirred. An addition of sodium bicarbonate (0.0096 g, 0.115 mmol) was made to the flask after 5 hours, followed by saturated sodium bicarbonate solution (1 mL). The solution was transferred to a separatory funnel, extracted using diethyl ether (10 mL), and washed with saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic layers were washed with saturated sodium chloride solution (20 mL), dried over magnesium sulfate, and filtered. After concentration by rotary evaporation, the acetylated product **62** remained as an oil (0.0996 g, 91% yield). ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.78 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 7.4 Hz,

2H), 3.81 (s, 2H), 3.75 (s, 2H), 2.44 (s, 3H), 1.87 (s, 3H), 0.89 (s, 6H); ^{13}C NMR (126 MHz, Acetone-d_6) δ 169.8, 145.1, 133.1, 130.1, 128.0, 74.6, 67.8, 34.8, 20.7, 20.6, 20.6.

4.9 Synthesis of Compound 69

4.9.1 Initial Reaction Sequence to Synthesize Compound 69



60 68 69

Figure 52. Initial Reaction Sequence to Synthesize Compound **69**

A solution of dimethyl diol **60** (0.200 g, 1.92 mmol) in dichloromethane (4.0 mL) was prepared in a flame-dried 10 mL round bottom flask. The flask was cooled with a -5^{o}C dry ice and isopropanol bath before pyridine (0.311 mL, 3.84 mmol) was added, followed by the dropwise addition of methylsulfonyl chloride (0.149 mL, 1.92 mmol). After 4 hours at 0°C, the reaction solution was diluted with ethyl acetate, transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 x 10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (20→100% ethyl acetate, 0.1% triethylamine in hexanes) but side products could not be completely removed to obtain an accurate yield. The crude mesylated product **68** was obtained (0.3835 g, crude >99% yield).

In a flame-dried 25 mL round bottom flask was prepared a solution of mesylated dimethyl **68** (0.384 g, 2.10 mmol) in dichloromethane (14.0 mL), to which 4-

dimethylaminopyridine (0.0123 g, 0.101 mmol), triethylamine (0.295 mL, 2.12 mmol), and acetic anhydride (0.337 mL, 3.57 mmol) were added. The reaction solution was stirred at room temperature. After 5 hours, sodium bicarbonate (0.0558 g, 0.664 mmol) was added to the solution along with saturated sodium bicarbonate solution (2 mL). Once this had stirred for 10 minutes, the solution was diluted with diethyl ether, transferred to a separatory funnel, and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted using diethyl ether (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The resulting organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (25→75% ethyl acetate, 0.1% triethylamine in hexanes) to yield acetylated product **69** (0.1586 g, overall 37% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.01 (s, 2H), 3.86 (s, 2H), 3.08 (s, 3H), 2.00 (s, 3H), 0.98 (s, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 170.1, 74.4, 68.0, 36.0, 34.9, 20.6, 19.8.

4.9.2 Alternative Sequence for Synthesis of Compound 69

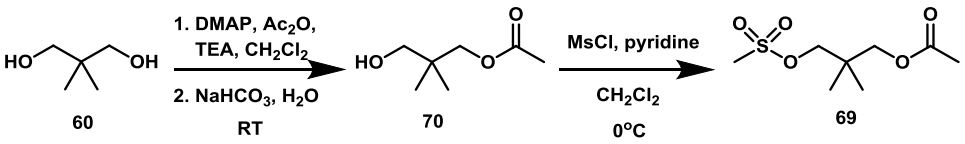


Figure 53. Alternative Sequence for Synthesis of Compound **69**

In a flame-dried 50 mL round bottom flask was made a solution of dimethyl diol **60** (0.3000 g, 2.88 mmol) in dichloromethane (19 mL), to which 4-dimethylaminopyridine (0.0169 g, 0.138 mmol), triethylamine (0.401 mL, 2.88 mmol), and acetic anhydride (0.272 mL, 2.88 mmol) were added. The reaction solution was stirred at room

temperature. After 6 hours, sodium bicarbonate (0.0760 g, 0.910 mmol) was added to the solution, along with saturated sodium bicarbonate solution (3 mL). Once this had stirred for 10 minutes, the solution was diluted with diethyl ether, then transferred to a separatory funnel and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted using diethyl ether (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The resulting organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (30→75% ethyl acetate, in hexanes) to yield acetylated product **70** (0.2157 g, 51% yield).

A solution of acetylated product **70** (0.100 g, 0.684 mmol) in dichloromethane (1.5 mL) was prepared in a flame-dried 10 mL round bottom flask. The flask was cooled with a -5°C dry ice and isopropanol bath before pyridine (0.111 mL, 1.368 mmol) was added, followed by the dropwise addition of methylsulfonyl chloride (0.089 mL, 1.163 mmol). After 4 hours at 0°, the reaction solution was diluted with ethyl acetate (5 mL), transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 x 10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated crude residue of product **69** was obtained (0.1450 g, crude 95% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.01 (s, 2H), 3.86 (s, 2H), 3.08 (s, 3H), 2.00 (s, 3H), 0.98 (s, 6H).

4.9.3 Acetylated Intermediate 70 through Alternative Protocol

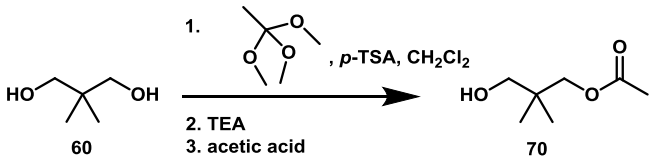


Figure 54. Acetylation to Intermediate **70** through Alternative Protocol

To a flame-dried 10 mL round bottom flask was added p-toluenesulfonic acid (monohydrate, 0.0006 g, 0.003 mmol) and dichloromethane (6.10 mL), followed by dimethyl diol **60** (0.500 g, 4.80 mmol). The solution was heated to 35°C before the diol was fully dissolved. Trimethyl orthoacetate (0.983 mL, 7.20 mmol) was added once the diol dissolved, then reaction solution was stirred at room temperature. After 1 hour, triethylamine (0.07 mL) was added to quench the reaction solution and stirred for several minutes before the solution was condensed through rotary evaporation. The resulting residue was returned to inert atmosphere and acetic acid (1.50 mL) was added. This solution was stirred at room temperature for 30 minutes. The reaction solution was then diluted with dichloromethane (10 mL), added to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 x 10 mL). The combined aqueous layers were extracted with dichloromethane (2 x 10 mL), then the combined organic phases were washed with saturated sodium chloride solution (20 mL). The organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. Analysis of the ^{13}C and ^{1}H NMR spectra showed very little contamination and so no purification was required (0.4781 g, 68% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 3.83 (s, 2H), 3.68 (t, J = 5.7 Hz, 1H), 3.29 (d, J = 5.7 Hz, 2H), 1.97 (s, 3H), 0.86 (s, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 170.4, 69.1, 67.5, 35.9, 20.9, 19.9.

4.9.4 Mesylation of Alternate Protocol Product to Compound 69

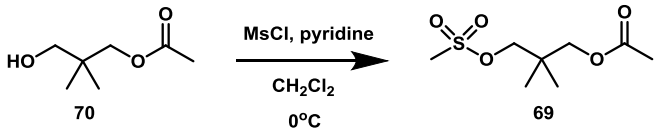


Figure 55. Mesylation of Alternate Protocol Product to Compound **69**

A solution of acetylated compound **66** (0.478 g, 3.27 mmol) in dichloromethane (6.8 mL) was made in a flame-dried 15 mL round bottom flask. The flask was cooled to 2°C with an ice and water bath before pyridine (0.661 mL, 8.18 mmol) was added, followed by the dropwise addition of methylsulfonyl chloride (0.633 mL, 8.18 mmol). After 5 hours at 2°C, the reaction solution was diluted with ethyl acetate, transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The crude residue of product **65** was collected. ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.01 (s, 2H), 3.86 (s, 2H), 3.08 (s, 3H), 2.01 (s, 3H), 0.98 (s, 6H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 170.1, 74.4, 68.0, 36.0, 34.9, 20.6, 19.8.

4.10 Synthesis of Compound 73

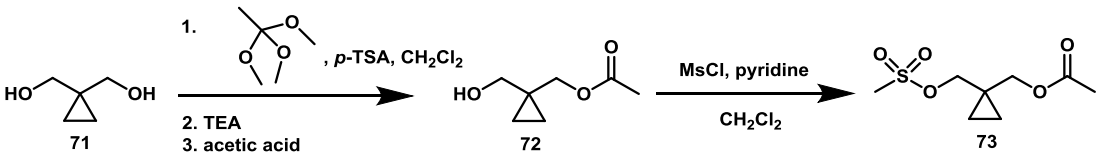


Figure 56. Synthesis of Compound **73**

To a flame-dried 10 mL round bottom flask was added p-toluenesulfonic acid (monohydrate, 0.0004 g, 0.002 mmol) and dichloromethane (3.72 mL), followed by cyclopropyl diol **71** (0.282 mL, 2.94 mmol) and trimethyl orthoacetate (0.602 mL, 4.41 mmol). The reaction solution was stirred at room temperature. After 1 hour, triethylamine (0.04 mL) was added to quench the reaction solution and stirred for several minutes before the solution was condensed through rotary evaporation. The resulting residue was returned to inert atmosphere and acetic acid (0.925 mL) was added. This solution was stirred at room temperature for 30 minutes. The reaction solution was then diluted with dichloromethane (10 mL) , added to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 x 10 mL). The combined aqueous layers were extracted with dichloromethane (2 x 10 mL), then the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The residue was purified by flash column chromatography on silica gel (10→45% ethyl acetate in hexanes) to yield acylated product **72** (0.3190 g, 75% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.02 (s, 2H), 3.42 (s, 2H), 2.07 (s, 3H), 0.53 (m, 4H);^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.8, 68.5, 66.8, 22.4, 21.1, 9.0.

A solution of acetylated compound **72** (0.100 g, 0.694 mmol) in dichloromethane (1.5 mL) was prepared in a flame-dried 10 mL round bottom flask. The flask was cooled to 0°C with an ice and water bath before pyridine (0.168 mL, 2.08 mmol) was added, followed by the dropwise addition of methylsulfonyl chloride (0.161 mL, 2.08 mmol). After 5 hours, the reaction solution was diluted with ethyl acetate, transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic phase was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The crude residue was collected and used for the alkylation attempt (crude 0.2055 g, >99% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 4.13 (s, 2H), 3.98 (s, 2H), 3.07 (s, 3H), 2.00 (s, 3H), 0.70 (s, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.1, 67.3, 66.0, 37.7, 21.0, 19.9, 10.0.

4.11 Synthesis of Compound 53

4.11.1 Dialkylated Intermediate 76

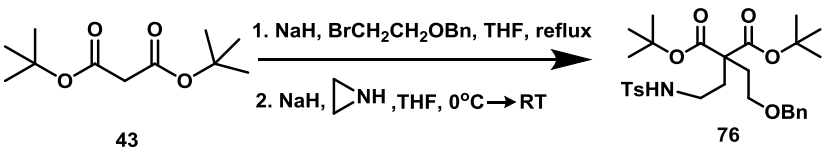


Figure 57. Synthesis of Dialkylated Intermediate **76**

To a flame-dried 25 mL round bottom was added sodium hydride (60% in mineral oil, 0.278g, 6.90 mmol) and tetrahydrofuran (16.40 mL). After stirring for several minutes, di-*tert*-butyl malonate (1.55 mL, 6.90 mmol) was added dropwise to the flask. The solution stirred for about 10 minutes before the bubbling ceased and appearance

became less cloudy, then benzyl 2-bromoethylether (1.10 mL, 6.90 mmol) was added dropwise. The reaction flask was heated to 60°C with an oil bath and stirred. After 27 hours, the flask was removed from the oil bath and saturated ammonium chloride solution was added until bubbling upon addition ceased. The reaction solution was transferred to a separatory funnel and deionized water (10 mL) was added. The resulting organic phase was washed with deionized water (2 x 10 mL), then saturated sodium chloride solution (10 mL) before being collected. The combined aqueous phases were extracted with diethyl ether (2 x 10 mL) and each organic phase was washed with sodium chloride solution (10 mL) before the combined organic layers were washed with sodium chloride solution (20 mL), dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (5→25% ethyl acetate in hexanes) yielding the monoalkylated intermediate (1.7428 g, 72% yield).

A solution of sodium hydride (60% in mineral oil, 0.382 g, 9.56 mmol) in tetrahydrofuran (6.37 mL) was made in a flame-dried 25 mL round bottom flask. The solution was stirred for several minutes before the monoalkylated product (1.67 g, 4.78 mmol) dissolved in tetrahydrofuran (3.68 mL) was added to it and the flask was cooled to 2°C with an ice water bath. Once bubbling of the solution was no longer seen, *N*-tosyl aziridine (0.804 g, 4.08 mmol) dissolved in tetrahydrofuran (4.21 mL) was slowly added and stirred. After 46 hours, the flask was removed from the room temperature water bath and saturated ammonium chloride solution was added to the reaction solution until bubbling ceased. The solution was transferred to a separatory funnel and washed with deionized water (10 mL). The organic phase was washed with deionized water (2 x 10 mL) then saturated sodium chloride solution (10 mL) before being collected. The

combined aqueous layers were extracted with diethyl ether (2 x 10 mL) and each organic layer was washed with sodium chloride solution collection. The combined organic layers were washed with sodium chloride solution (20 mL) and the resulting organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (20→100% ethyl acetate in hexanes) yielding dialkylated product **76** (1.3432 g, 51% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.63 (m, 2H), 7.31 (m, 6H), 7.23 (s, 1H), 4.75 (t, *J* = 5.9 Hz, 1H), 4.40 (s, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 2.89 (td, *J* = 7.3, 6.0 Hz, 2H), 2.39 (s, 3H), 2.09 (t, *J* = 6.4 Hz, 2H), 2.02 (t, *J* = 7.3 Hz, 2H), 1.37 (s, 18H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 143.3, 137.9, 136.8, 129.7, 128.5, 128.0, 127.9, 127.2, 82.0, 73.3, 66.1, 56.5, 39.3, 32.4, 27.8, 21.6, 21.2.

4.11.2 Debenzylated intermediate 74

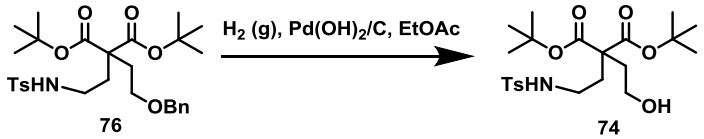


Figure 58. Synthesis of Debenzylated Intermediate **74**

To a flame-dried 25 mL round bottom flask was added a solution of dialkylated product **76** (0.484 g, 0.884 mmol) in ethyl acetate (17.7 mL), followed by palladium hydroxide on carbon (0.0620 g, 0.442 mmol). Hydrogen gas was flushed through the flask two times by evacuation of the gas with the house vacuum, then the third balloon was used to keep the reaction under hydrogen gas for its duration. The solution was stirred at room temperature overnight, after which time the hydrogen gas was removed from the flask using the house vacuum. The solution was then filtered through celite and

rinsed with ethyl acetate (20 mL). The filtered solution was analyzed using gas chromatography and showed only about 50% conversion to product. The solution was condensed by rotary evaporation, added to a new flame-dried 25 mL round bottom flask, and the same portions of palladium hydroxide on carbon and ethyl acetate were added. The flask was once again flushed twice with hydrogen gas before. Following another 24 hour reaction the solution filtered through celite and gas chromatography analysis showed nearly complete conversion. The solution was again condensed through rotary evaporation and the residue was purified by flash column chromatography on silica gel (25→75% ethyl acetate in hexanes) yielding debenzylated product **74** as a white solid (0.1777 g, 44% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.70 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 6.43 (t, J = 6.2 Hz, 1H), 3.58 (t, J = 5.2 Hz, 1H), 3.48 (q, J = 6.5 Hz, 2H), 2.83 (m, 4H), 2.39 (s, 3H), 1.95 (t, J = 7.1 Hz, 2H), 1.37 (s, 18H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 169.9, 168.9, 147.1, 133.6, 129.6, 127.0, 80.9, 55.7, 52.7, 49.2, 43.8, 34.96, 27.1, 20.5.

4.11.3 Enantioenriched Monocyclized Intermediate 75

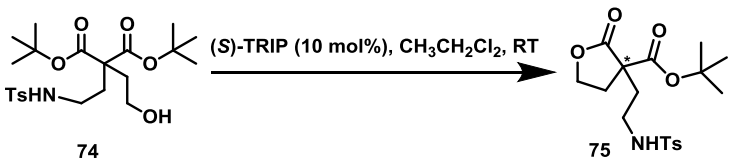


Figure 59. Synthesis of Enantioenriched Monocyclized Intermediate **75**

To a flame-dried 25 mL round bottom flask was added debenzylated product **74** (0.548g, 1.20 mmol) dissolved in dichloroethane (12 mL). S-TRIP catalyst (0.045 g, 0.060 mmol) was added and the solution was stirred at room temperature. After 7 days, the round bottom solution was diluted with ethyl acetate (10 mL), transferred to a

separatory funnel, and washed with deionized water (2 x 10 mL). The aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The resulting organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The concentrated residue was purified by flash column chromatography on silica gel (30→50% ethyl acetate in hexanes) to give monocyclic product **75** (0.1589 g, 35% yield). ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.71 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.30 (m, 2H), 3.09 (ddt, J = 12.7, 9.9, 5.7 Hz, 1H), 2.92 (ddt, J = 12.4, 10.0, 6.1 Hz, 1H), 2.63 (ddd, J = 13.3, 7.0, 3.1 Hz, 1H), 2.34 (dt, J = 13.2, 8.9 Hz, 1H), 2.17 (ddd, J = 13.9, 9.9, 5.5 Hz, 1H), 1.90 (ddd, J = 13.8, 10.1, 6.0 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, Acetone-d_6) δ 174.6, 168.4, 143.1, 137.9, 129.7, 127.0, 82.5, 66.3, 53.3, 39.4, 33.6, 32.0, 27.0, 20.6.

4.11.4 Compound 53

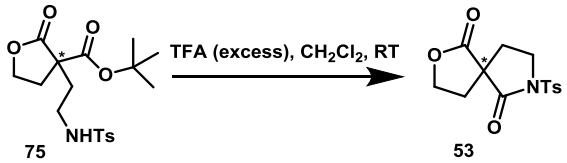


Figure 60. Cyclization to Compound **53**

In a flame-dried 15 mL round bottom flask was made a solution of monocyclic product **75** (0.158 g, 0.412 mmol) in dichloromethane (5.10 mL). To this solution trifluoroacetic acid (5.89 mL, 76.9 mmol) was added slowly before the solution was stirred at room temperature. After 47 hours, ethyl acetate (10 mL) was added to the reaction solution and the flask contents were transferred to a separatory funnel. The solution was washed with deionized water (20 mL), the aqueous layer was extracted

with ethyl acetate (2 x 10 mL), and the combined organic phases were washed with saturated sodium chloride solution (20 mL). The final organic layer was dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The crude spirocyclic product **53** was collected (0.1153 g, 90% crude yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.49 (dd, *J* = 16.5, 8.2 Hz, 1H), 4.32 (td, *J* = 8.7, 4.1 Hz, 1H), 4.04 (m, 2H), 2.73 (ddd, *J* = 13.0, 7.5, 4.1 Hz, 1H), 2.54 (ddd, *J* = 13.0, 6.8, 3.0 Hz, 1H), 2.43 (s, 3H), 2.18 (m, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.3, 170.1, 145.9, 134.2, 129.9, 128.2, 66.8, 53.0, 45.0, 32.1, 28.8, 21.9.

4.12 Synthesis of Compound 77

4.12.1 Dialkylated intermediate 80

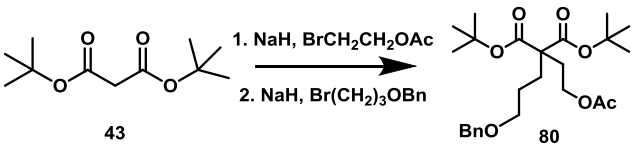


Figure 61. Synthesis of Dialkylated Intermediate **80**

A solution of sodium hydride (60% in mineral oil, 0.185 g, 4.62 mmol) in tetrahydrofuran (28 mL) was prepared in a flame-dried 50 mL round bottom flask under inert atmosphere and allowed to stir for several minutes. Di-*tert*-butyl malonate (1.00 g, 4.62 mmol) was added to the reaction flask dropwise and the solution was stirred at room temperature until the solution ceased bubbling and turned from cloudy to transparent. Once this change was observed, ethyl bromoacetate (0.501 mL, 4.62 mmol) was added dropwise to the flask and the reaction solution was stirred. After 3 days, saturated ammonium chloride solution was added to the flask until bubbling could no longer be seen and stirred for several minutes until the solution became transparent.

The solution was then transferred to a separatory funnel and deionized water (10mL) was added. The organic phase was washed with deionized water (2 x 10 mL) and saturated sodium chloride solution (10 mL). The combined aqueous layers were extracted with diethyl ether (2 x 10 mL) and each organic phase was washed with saturated sodium chloride solution (10 mL) before collection. The combined organic layers were washed with saturated sodium chloride solution (20 mL), dried over magnesium sulfate, and concentrated via rotary evaporation. The condensed residue was purified by flash column chromatography on silica gel (5→30% ethyl acetate in hexanes) to yield monoalkylated intermediate (0.8870 g, 64% yield).

Into a 10 mL flame-dried round bottom flask was added sodium hydride (60% in mineral oil, 0.0670 g, 1.69 mmol) and tetrahydrofuran (4.00 mL). Previously synthesized monoalkylated product (0.255 g, 0.843 mmol) was dissolved in tetrahydrofuran (2.00 mL) and added to the flask slowly. After the solution had ceased bubbling and become more transparent, benzyl-3-bromopropylether (0.149 mL, 0.843 mmol) was added slowly to the reaction solution before the flask was heated with a 55^{o}C oil bath. After 3 days, the flask was removed from the oil bath and saturated ammonium chloride solution (4 mL) was added to the reaction solution. After stirring for several minutes, the contents of the flask were transferred to a separatory funnel and additional ammonium chloride solution (10 mL) as well as deionized water (20 mL) were added. The resulting organic layer was washed with deionized water (2 x 10 mL) and then saturated sodium chloride solution (10 mL) before collection. The aqueous phase was extracted with diethyl ether (2 x 10 mL), each extraction washed with sodium chloride solution (10 mL) before collection. The collected organic layers were washed with sodium chloride solution (20 mL), dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The

concentrated residue was purified by flash column chromatography on silica gel (5→20% ethyl acetate in hexanes) to yield dialkylated product **80** (0.1632 g, 43% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.31 (m, 5H), 4.47 (s, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 6.5 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 1.98 (s, 3H), 1.90 (m, 2H), 1.43 (s, 18H);^{13}C NMR (101 MHz, Chloroform-d) δ 171.0, 170.4, 138.6, 128.4, 127.7, 127.6, 81.6, 72.9, 70.3, 60.8, 56.7, 30.7, 29.2, 28.0, 24.5, 21.0.

4.12.2 Alternative Alkylation Sequence to Compound 80

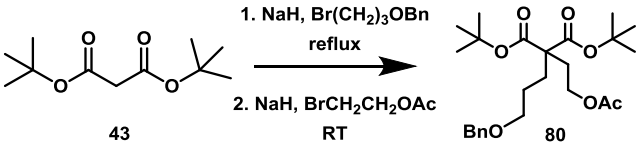


Figure 62. Alternative Alkylation Sequence to Compound **80**

Into a 10 mL flame-dried round bottom flask was added sodium hydride (60% in mineral oil, 0.0630 g, 1.58 mmol) and tetrahydrofuran (4.00 mL). Di-*tert*-butyl malonate (0.236 mL, 1.05 mmol) was added to the flask slowly. After the solution had ceased bubbling and become more transparent, benzyl-3-bromopropylether (0.250 mL, 1.58 mmol) was added slowly to the reaction solution before the flask was heated with a 55ºC oil bath. After 2 days, the flask was removed from the oil bath and saturated ammonium chloride solution (4 mL) was added to the reaction solution. After stirring for several minutes, the contents of the flask were transferred to a separatory funnel and additional ammonium chloride solution (10 mL) as well as deionized water (10 mL) were added. The resulting organic layer was washed with deionized water (2 x 10 mL), then with saturated sodium chloride solution (10 mL) before collection. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and each extraction was washed with sodium

chloride solution (10 mL) before collection. The collected organic layers were washed with sodium chloride solution (20 mL), dried over magnesium sulfate, filtered, and condensed by rotary evaporation. The crude residue was collected (0.5425 g, >99% crude yield).

A solution of sodium hydride (60% in mineral oil, 0.149 g, 3.72 mmol) in dimethylformamide (9 mL) was made in a flame-dried 25 mL round bottom flask under inert atmosphere and stirred for several minutes. Previously synthesized monoalkylated product (0.543 g, 1.49 mmol) was added to the reaction flask slowly and the solution was stirred at room temperature until the solution ceased bubbling and turned from cloudy to transparent. After 30 min, ethyl bromoacetate (0.410 mL, 3.72 mmol) was added dropwise to the flask. After 2 days, saturated ammonium chloride solution was added to the flask until bubbling could no longer be seen and allowed to stir for several minutes until the solution became transparent. The solution was then transferred to a separatory funnel and deionized water (10mL) was added. The organic phase was washed with deionized water (2 x 10 mL) and saturated sodium chloride solution (10 mL) before being collected. The combined aqueous layers were extracted with diethyl ether (2 x 10 mL), washing each organic phase with saturated sodium chloride solution (10 mL) before collection. The combined organic layers were washed with saturated sodium chloride solution (20 mL), dried over magnesium sulfate, and concentrated via rotary evaporation. Crude residue of product **80** was collected (0.6281 g, 93% crude yield).

4.12.3 Debenzylation and Cyclization to Compound 77

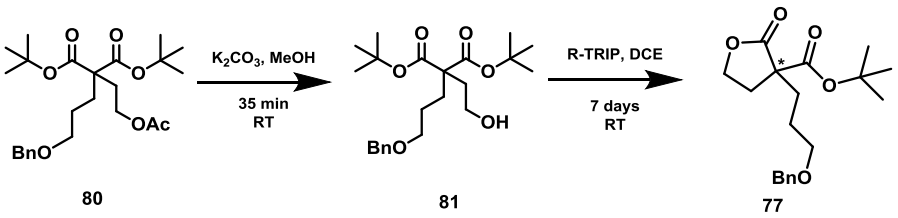


Figure 63. Debenzylation and Enantioenriched Cyclization to Intermediate **77**

A solution of dialkylated product **80** (0.163 g, 0.362 mmol) in methanol (4.70 mL) was made in a flame-dried 10 mL round bottom flask before potassium carbonate (0.200 g, 1.45 mmol) was added. Following the carbonate addition, the reaction solution was stirred at room temperature. After 35 minutes, the contents of the flask were transferred to a separatory funnel. Product was extracted with dichloromethane (10 mL) and washed with deionized water (20 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the organic phases were combined. The collected organic layers were washed with saturated sodium chloride solution (20 mL) before being dried over magnesium sulfate, filtered, and condensed through rotary evaporation to yield deprotected product **81** (0.1296 g, 88% yield).

A solution of *R*-TRIP catalyst (0.012 g, 0.016 mmol) in dichloromethane (3.97 mL) was made in a flame-dried 10 mL round bottom flask. Deprotected product **81** (0.130 g, 0.317 mmol) was added slowly to the solution and the reaction was stirred at room temperature. After 7 days, ethyl acetate (10 mL) was added to the solution and it was washed with deionized water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the organic layers were combined, washed with saturated sodium chloride solution (20 mL), then the resulting organic phase was dried over

magnesium sulfate. After being filtered, the solution was condensed through rotary evaporation. The condensed residue was purified by column chromatography on silica gel (15→50% ethyl acetate in hexanes) to yield monocyclized product **77** (0.0278 g, 26% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32(m, 5H), 4.49 (s, 2H), 4.30 (dd, *J* = 8.9, 5.2 Hz, 2H), 3.49 (td, *J* = 6.8, 6.2, 1.8 Hz, 2H), 2.65 (dt, *J* = 13.1, 4.8 Hz, 1H), 2.21 (dt, *J* = 12.8, 9.0 Hz, 1H), 2.12 (ddd, *J* = 13.3, 12.2, 4.1 Hz, 1H), 1.83 (ddd, *J* = 13.4, 12.1, 4.3 Hz, 1H), 1.75 (m, 1H), 1.58 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 175.3, 168.7, 138.4, 135.9, 128.5, 127.8, 83.1, 73.0, 70.0, 66.2, 54.7, 32.0, 27.9, 25.2, 22.9.

REFERENCES

(1) Thomas, J. P.; Baughn, C. O.; Wilkinson, R. G.; Shepherd, R. G. *Am. Rev. Respir. Dis.* **1961**, *83* (6), 891–893.

(2) Leibold, J. E. *Ann. N. Y. Acad. Sci.* **1966**, *135* (2), 904–909.

(3) Carr, R. E.; Henkind, P. *Arch. Ophthalmol.* **1962**, *67* (5), 566–571.

(4) Chhabra, N.; Aseri, M. L.; Padmanabhan, D. *Int. J. Appl. Basic Med. Res.* **2013**, *3* (1), 16.

(5) Lim, S. *Ann.-Acad. Med. Singap.* **2006**, *35* (4), 274–278.

(6) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109* (7), 3012–3043.

(7) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55* (15), 4512–4515.

(8) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118* (38), 9202–9203.

(9) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2* (16), 2545–2548.

(10) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44* (26), 3974–4001.

(11) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343* (1), 5–26.

(12) Petersen, K. S. *Tetrahedron Lett.* **2015**, *56* (47), 6523–6535.

(13) Bertelsen, S.; Anker Jørgensen, K. *Chem. Soc. Rev.* **2009**, *38* (8), 2178–2189.

(14) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111* (5), PR110-PR180.

(15) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45* (24), 3909–3912.

(16) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129* (40), 12084–12085.

(17) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem. – Eur. J.* **2011**, *17* (31), 8524–8528.

(18) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43* (12), 1566–1568.

(19) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126* (17), 5356–5357.

(20) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395–456.

(21) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132* (12), 4056–4057.

(22) Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S. *Org. Lett.* **2013**, *15* (6), 1266–1269.

(23) Wilent, J.; Petersen, K. S. *J. Org. Chem.* **2014**, *79* (5), 2303–2307.

(24) Zhao, Y.; Zhang, X.; Li, J.; Bian, Y.; Sheng, M.; Liu, B.; Fu, Z.; Zhang, Y.; Yang, B. *PLOS ONE* **2016**, *11* (2), e0149386.

(25) Otsuka, H.; Akiyama, T.; Kawai, K.-I.; Shibata, S.; Inoue, O.; Ogihara, Y. *Phytochemistry* **1978**, *17* (8), 1349–1352.

(26) Huang, L.; Kashiwada, Y.; Cosentino, L. M.; Fan, S.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1994**, *4* (4), 593–598.

(27) Tang, J.; Qian, K.; Zhang, B.-N.; Chen, Y.; Xia, P.; Yu, D.; Xia, Y.; Yang, Z.-Y.; Chen, C.-H.; Morris-Natschke, S. L.; Lee, K.-H. *Bioorg. Med. Chem.* **2010**, *18* (12), 4363–4373.

(28) Xie, L.; Crimmins, M. T.; Lee, K.-H. *Tetrahedron Lett.* **1995**, *36* (26), 4529–4532.

(29) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1999**, *42* (14), 2662–2672.

(30) Chen, Y.; Cheng, M.; Liu, F.; Xia, P.; Qian, K.; Yu, D.; Xia, Y.; Yang, Z.-Y.; Chen, C.-H.; Morris-Natschke, S. L.; Lee, K.-H. *Eur. J. Med. Chem.* **2011**, *46* (10), 4924–4936.

(31) Mateos, A. F.; Martín de la Nava, E. M.; González, R. R. *J. Org. Chem.* **2001**, *66* (23), 7632–7638.

(32) Jeong, B.-S.; Choi, N. S.; Ahn, S. K.; Bae, H.; Kim, H. S.; Kim, D. *Bioorg. Med. Chem. Lett.* **2005**, *15* (15), 3580–3583.

(33) Lee, S.; Paek, S.-M.; Yun, H.; Kim, N.-J.; Suh, Y.-G. *Org. Lett.* **2011**, *13* (13), 3344–3347.

(34) Kavanagh, Y.; Chaney, C. M.; Muldoon, J.; Evans, P. *J. Org. Chem.* **2008**, *73* (21), 8601–8604.

(35) Shaw, D. E.; Fenton, G.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1994**, No. 21, 2447–2448.

(36) Gay, M.; Montana, A. M.; Moreno, V.; Font-Bardia, M.; Solans, X. *Chem. - Eur. J.* **2005**, *11*, 2130–2134.

(37) Mari, S.; Posteri, H.; Marcou, G.; Potenza, D.; Micheli, F.; Canada, F. J.; Jimenez-Barbero, J.; Bernardi, A. *Eur. J. Org. Chem.* **2004**, (24), 5119–5125.

(38) Bouhadir, K. H.; Aleiwe, B. A.; Fares, F. A. *Molecules* **2011**, *17* (1), 1–14.

(39) Nenaah, G. E. *Nat. Prod. Res.* **2014**, *28* (24), 2245–2252.

(40) Ammar, M. I.; Nenaah, G. E.; Mohamed, A. H. H. *Crop Prot.* **2013**, *49*, 21–25.

(41) Cheeke, P.; Piacente, S.; Oleszek, W. *J. Inflamm.* **2006**, *3*, 6.

(42) Piacente, S.; Montoro, P.; Oleszek, W.; Pizza, C. *J. Nat. Prod.* **2004**, *67* (5), 882–885.

(43) Olas, B.; Wachowicz, B.; Stochmal, A.; Oleszek, W. *Nutrition* **2003**, *19* (7–8), 633–640.

(44) Oleszek, W.; Sitek, M.; Stochmal, A.; Piacente, S.; Pizza, C.; Cheeke, P. *J. Agric. Food Chem.* **2001**, *49* (2), 747–752.

(45) Nakashima, Y.; Jin, Y.; Konobe, M. Cyclohexanone compounds and herbicides comprising the same. U. S. Patent 9101140 B2, August 11, 2015.

(46) Garner, P.; Anderson, J. T.; Cox, P. B.; Klippenstein, S. J.; Leslie, R.; Scardovi, N. *J. Org. Chem.* **2002**, *67* (17), 6195–6209.

(47) Liu, L. J.; Hong, J. H. *Nucleosides Nucleotides Nucleic Acids* **2010**, *29* (3), 257–266.

(48) Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133* (6), 1690–1693.

(49) Li, C.; Prichard, M. N.; Korba, B. E.; Drach, J. C.; Zemlicka, J. *Bioorg. Med. Chem.* **2008**, *16* (5), 2148–2155.

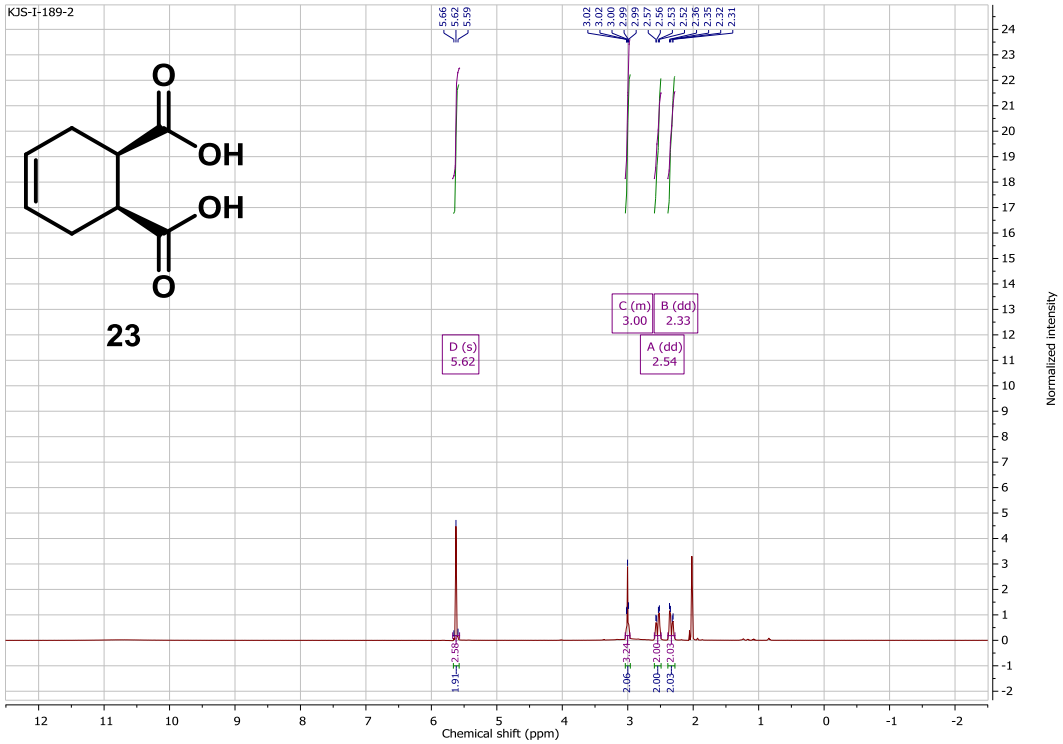
(50) Borisov, D. D.; Novikov, R. A.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2016**, *55* (40), 12233–12237.

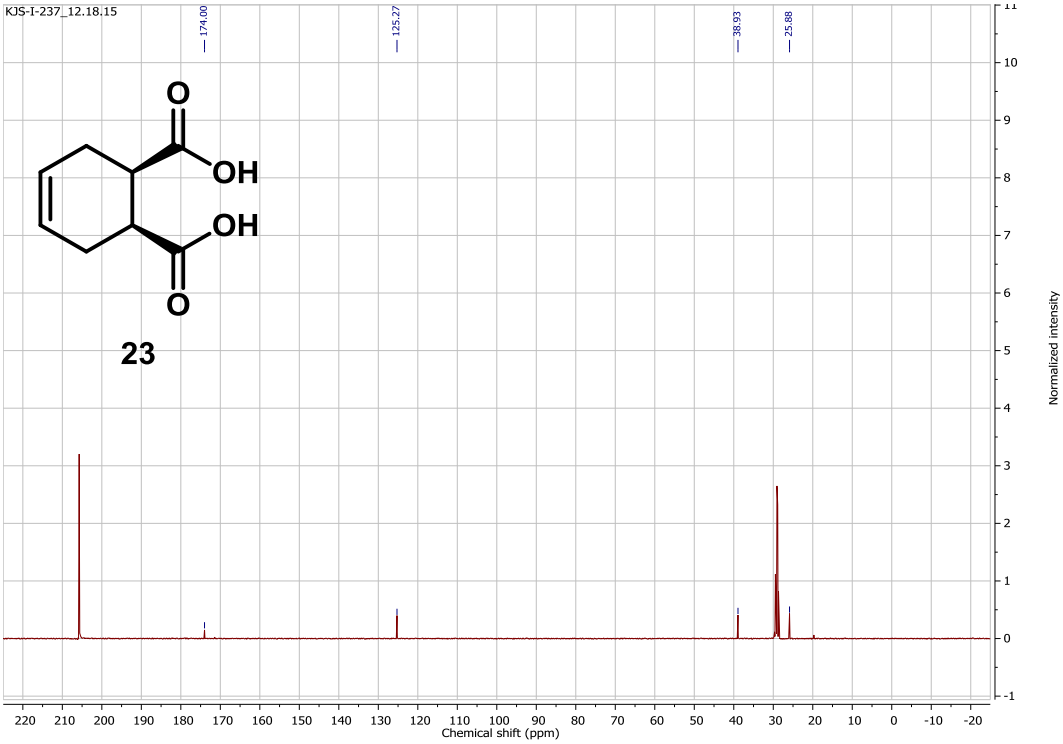
(51) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107* (0), 1080–1106.

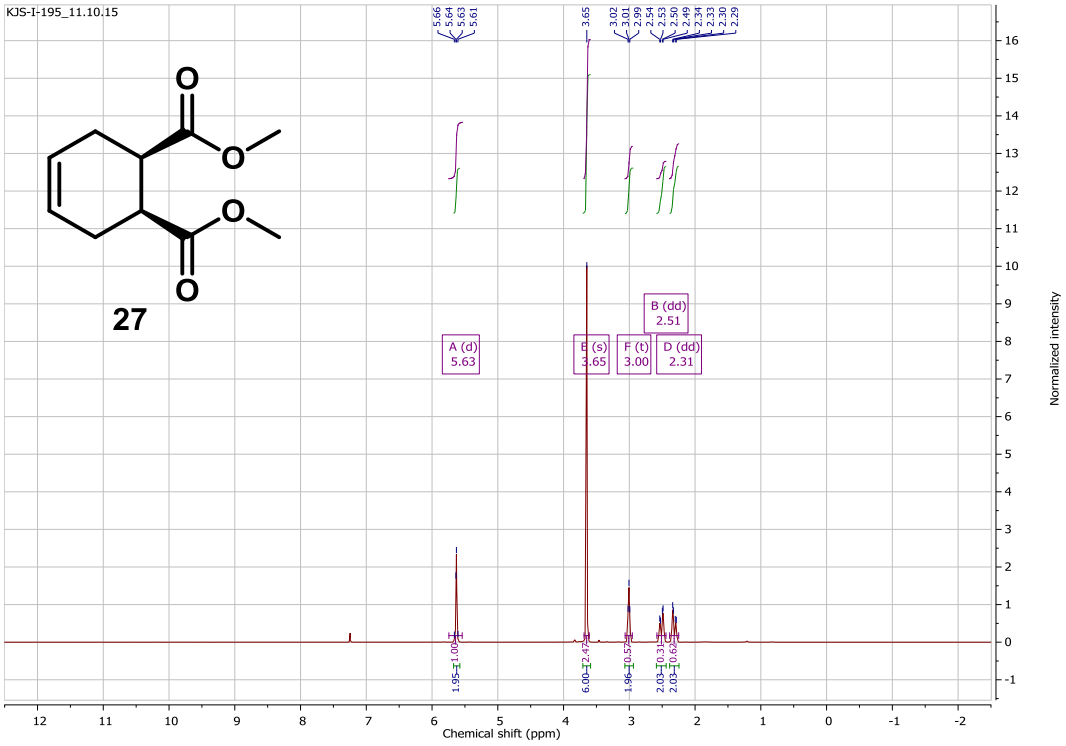
APPENDIX A

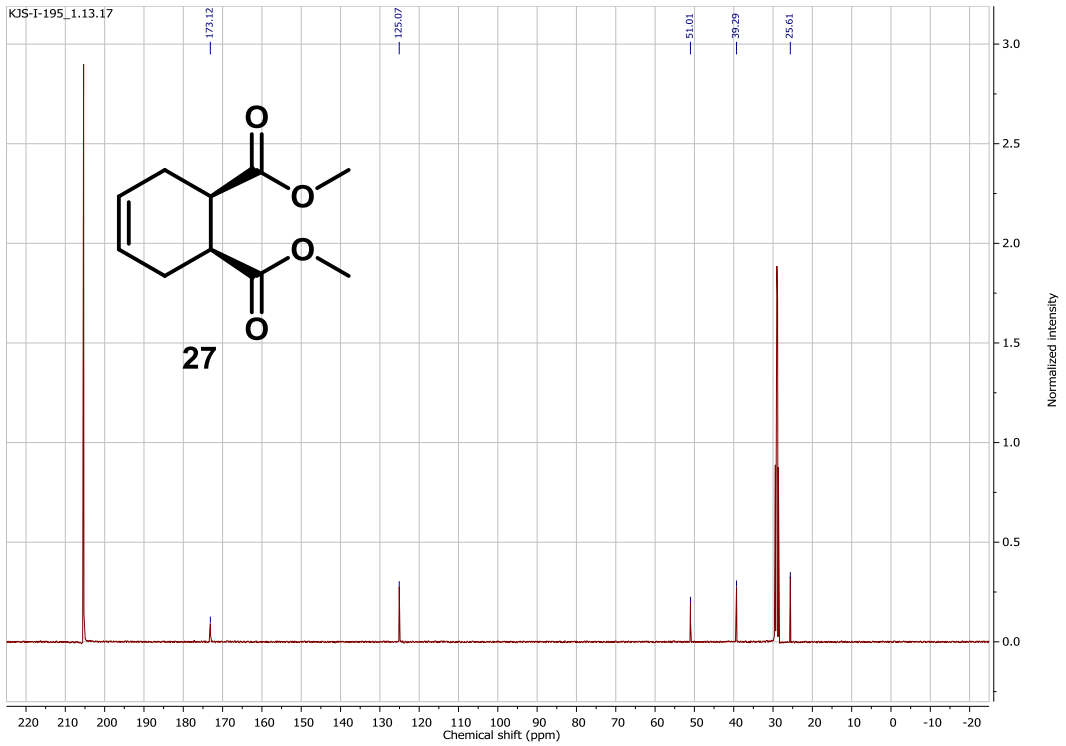
NMR SPECTRA

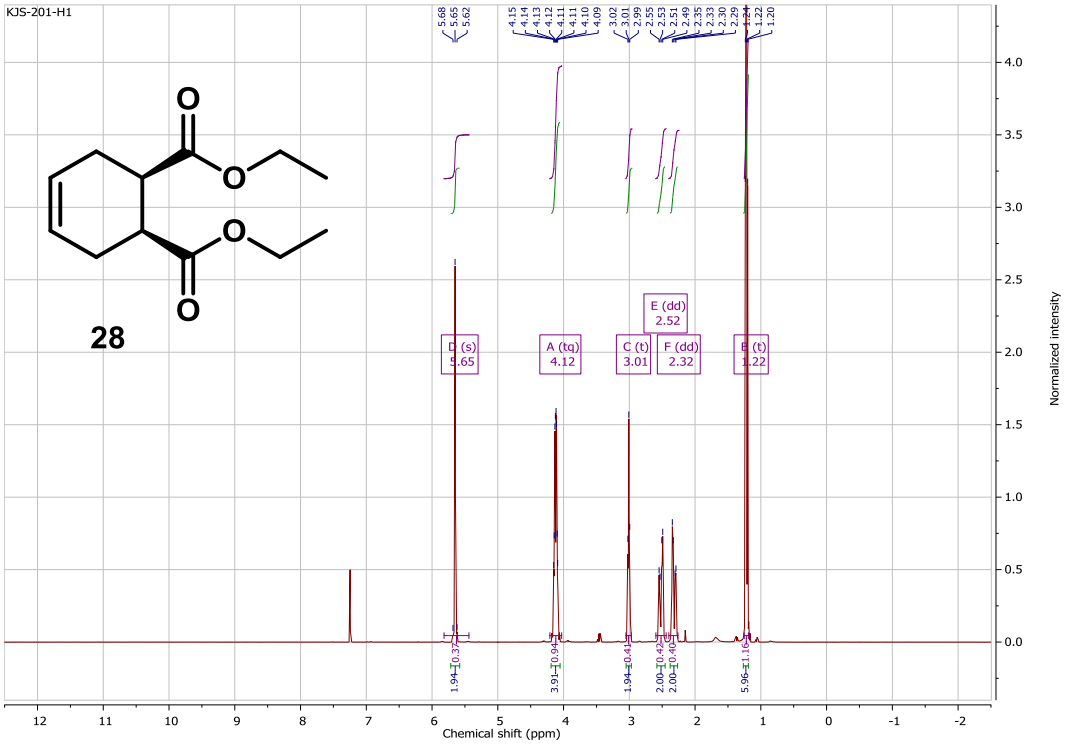
The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained via a JEOL 400 and 500 MHz spectrometer using chloroform-*d* or acetone-d_6 as a solvent at room temperature. The NMR chemical shifts (δ) are reported in parts per million (ppm).

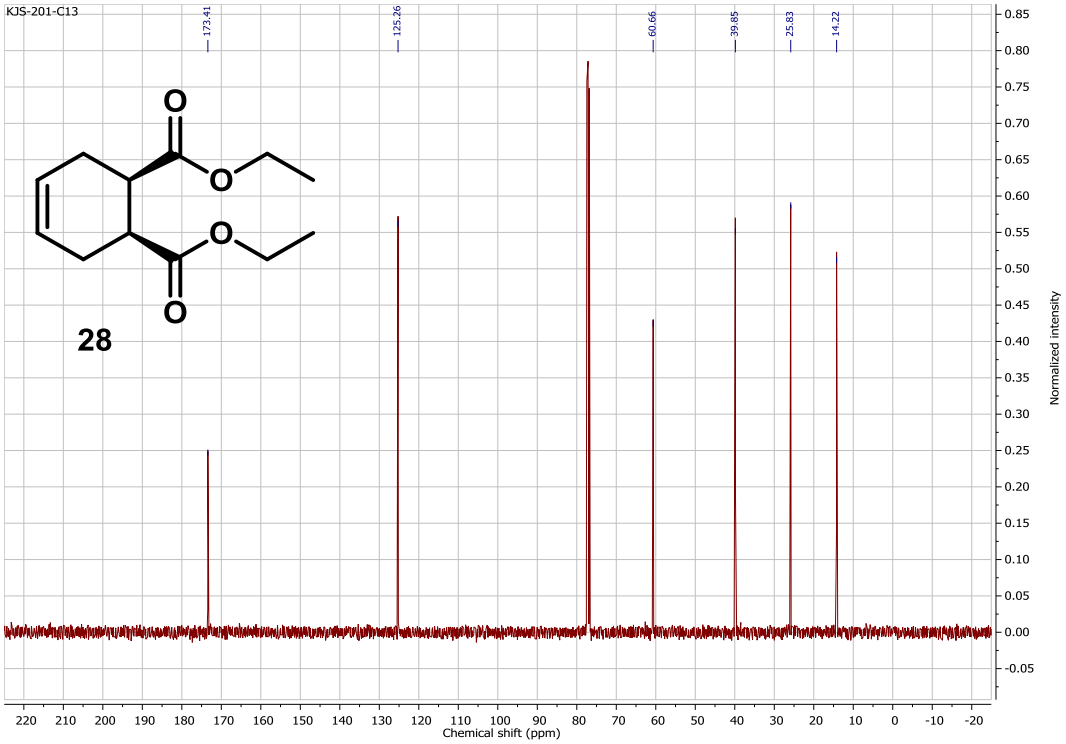

KJS-I-189-2
O
OH
OH
O
23
C (m) 3.00
B (dd) 2.33
D (s) 5.62
A (dd) 2.54
Chemical shift (ppm)
Normalized intensity

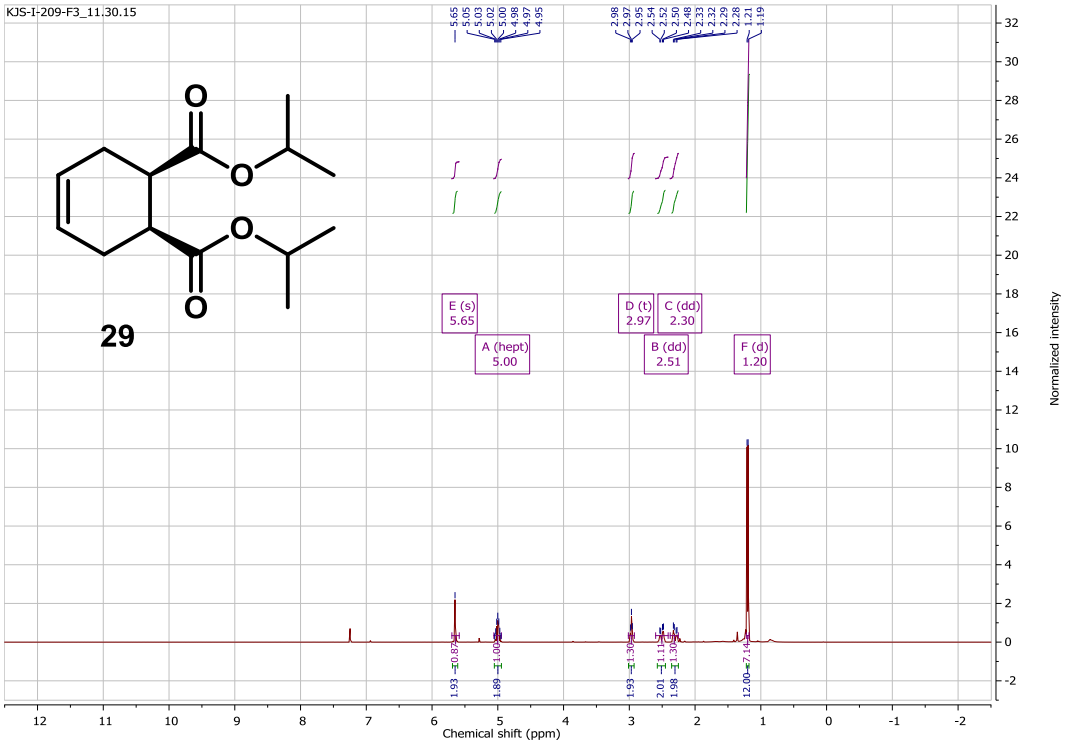

KJS-I-237_12.18.15
174.00
125.27
38.93
25.88
O
OH
OH
O
23
Chemical shift (ppm)
Normalized intensity


KJS-I-195_11.10.15
27
A (d) 5.63
B (dd) 2.51
E (s) 3.65
F (t) 3.00
D (dd) 2.31
Chemical shift (ppm)
Normalized intensity


KJS-I-195_1.13.17
27
Chemical shift (ppm)
Normalized intensity


KJS-201-H1
28
D (s)
5.65
A (tq)
4.12
C (t)
3.01
F (dd)
2.32
E (dd)
2.52
B (t)
1.22
Chemical shift (ppm)
Normalized intensity


KJS-201-C13
28
173.41
125.26
60.66
39.85
25.83
14.22
Chemical shift (ppm)
Normalized intensity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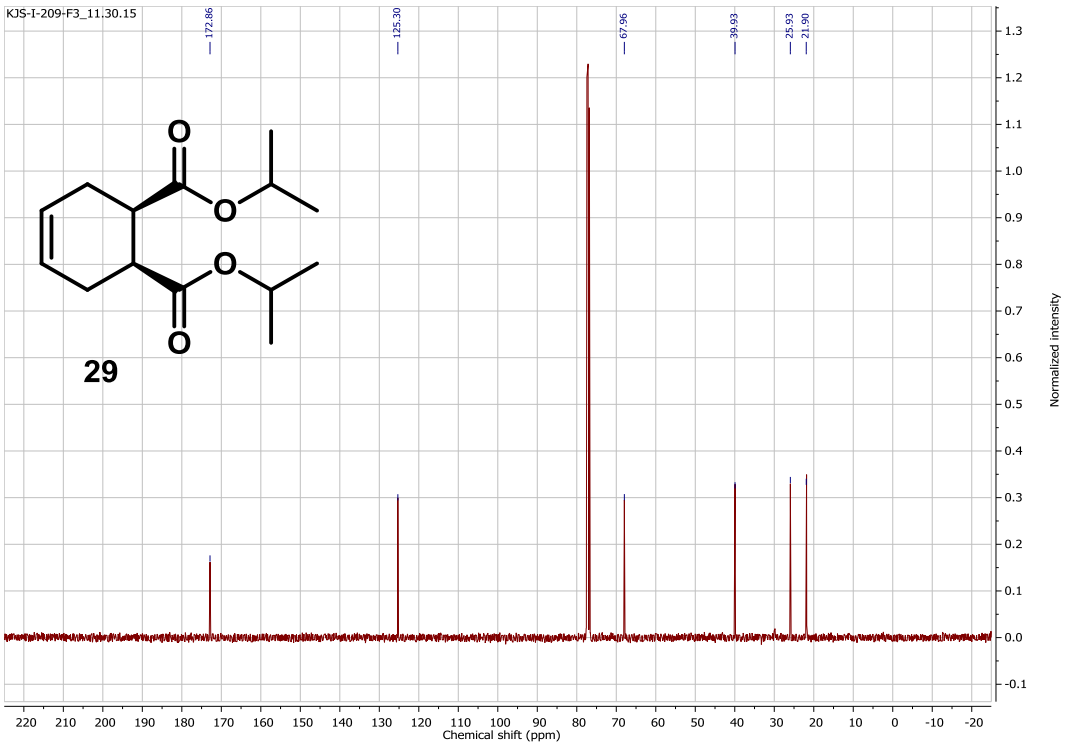
29
E (s)
5.65
A (hept)
5.00
D (t)
2.97
C (dd)
2.30
B (dd)
2.51
F (d)
1.20
Chemical shift (ppm)
Normalized intensity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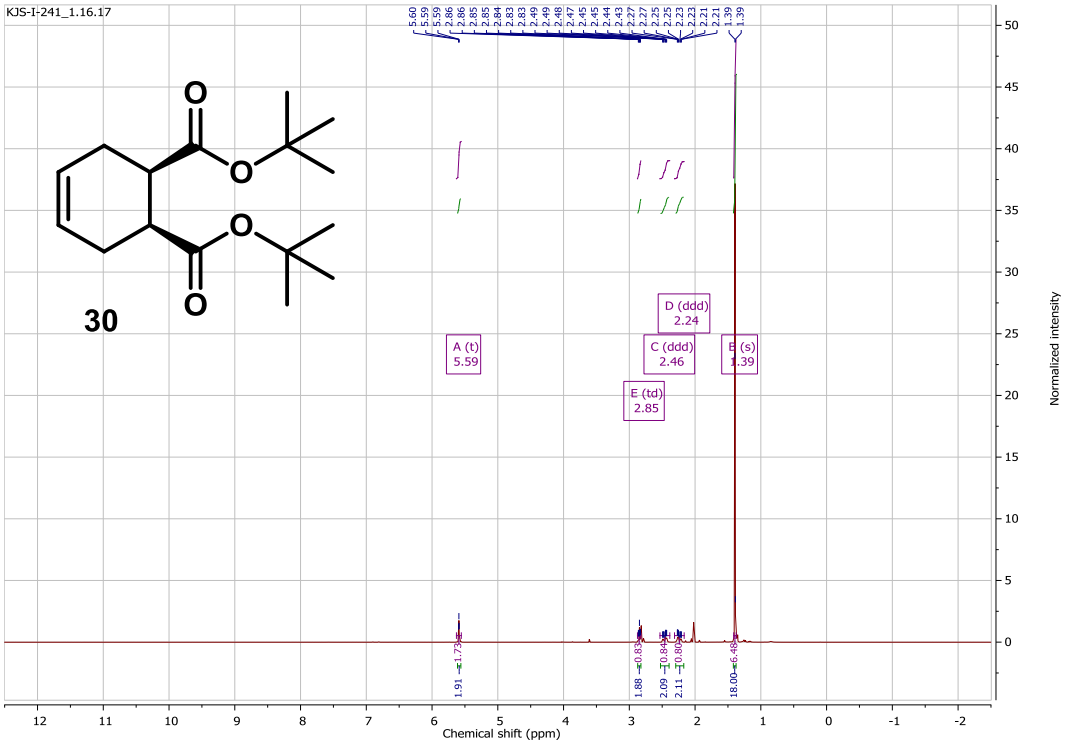
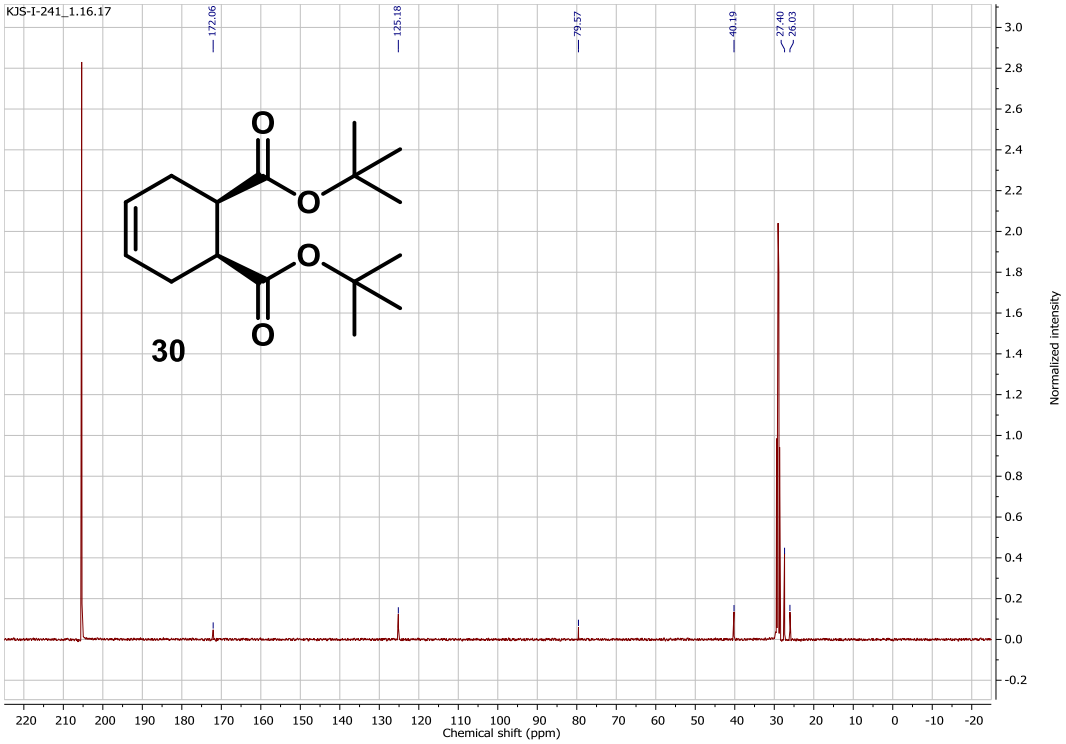
39.93
25.93
21.90
29
Chemical shift (ppm)
Normalized intensity


KJS-I-241_1.16.17
30
A (t)
5.59
D (ddd)
2.24
C (ddd)
2.46
B (s)
1.39
E (td)
2.85
Chemical shift (ppm)
Normalized intensity


KJS-I-241_1.16.17
172.06
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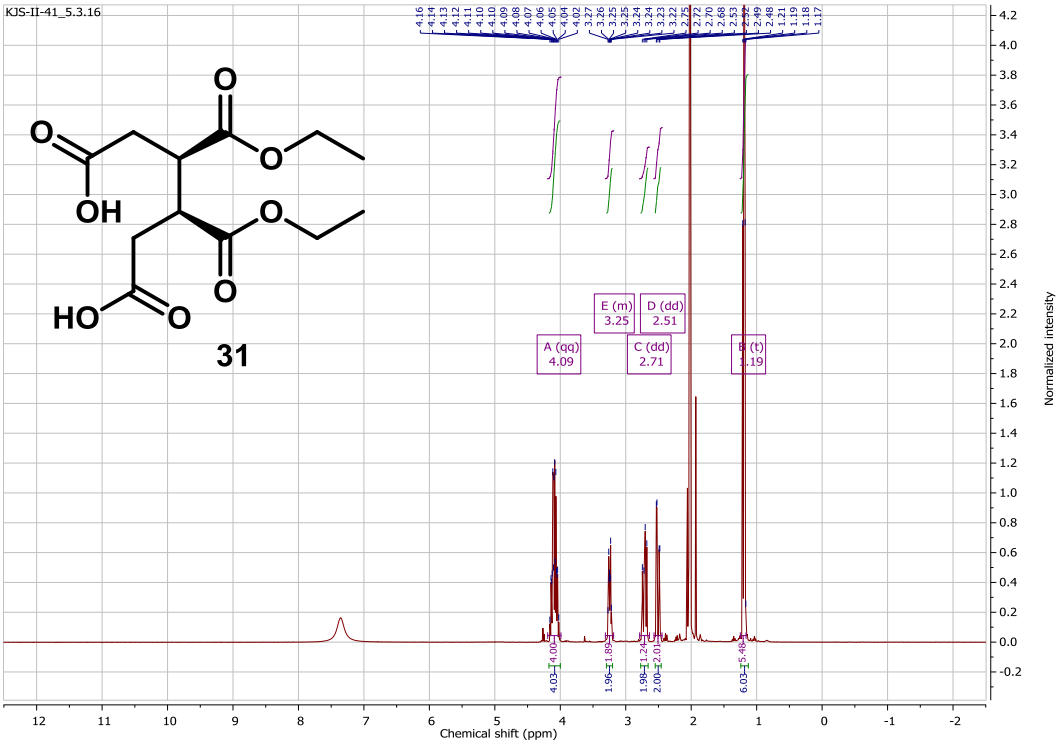
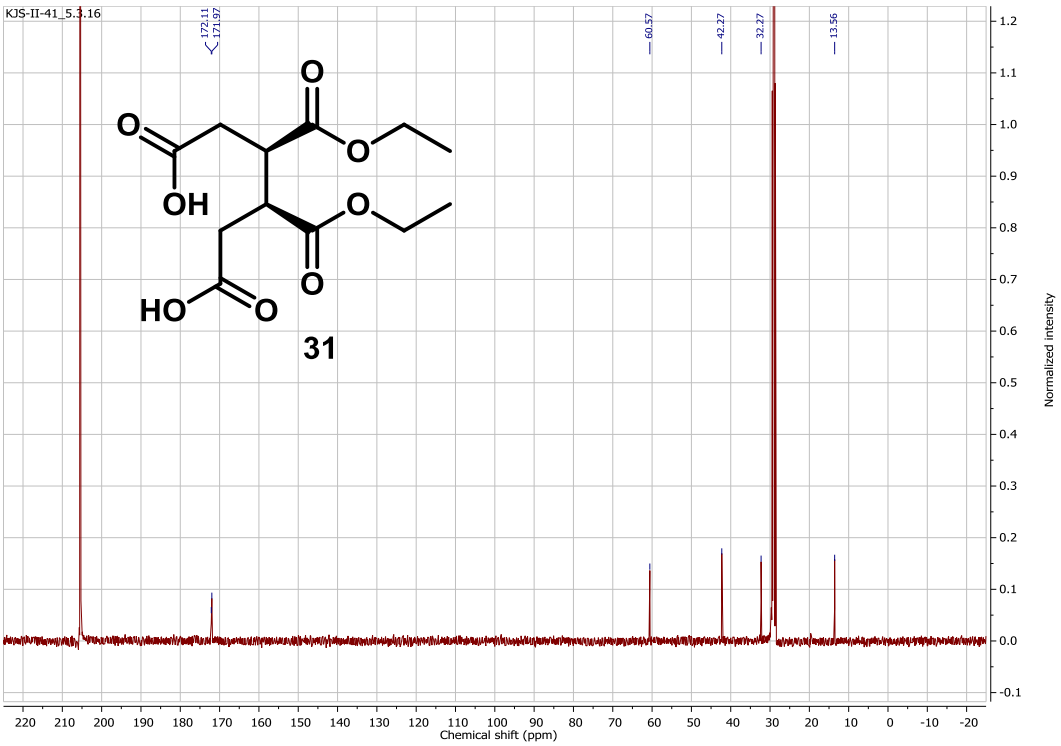
79.57
40.19
27.40
26.03
30
Chemical shift (ppm)
Normalized intensity


KJS-II-41_5.3.16
31
A (qq) 4.09
C (dd) 2.71
D (dd) 2.51
E (m) 3.25
Chemical shift (ppm)
Normalized intensity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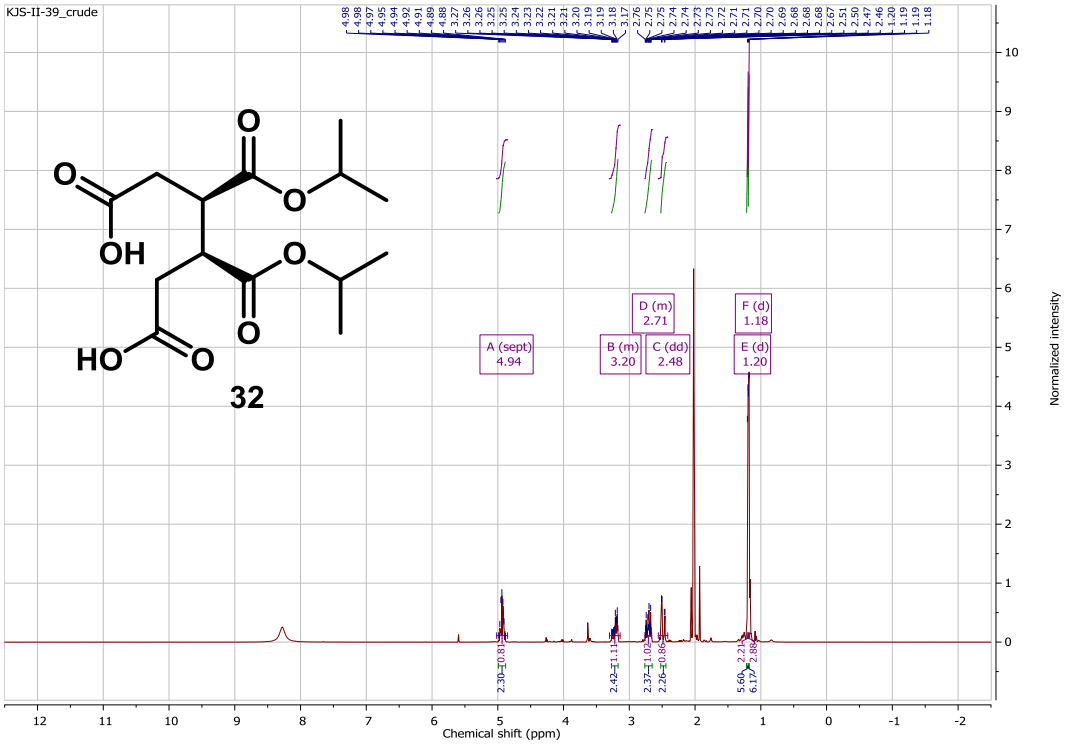
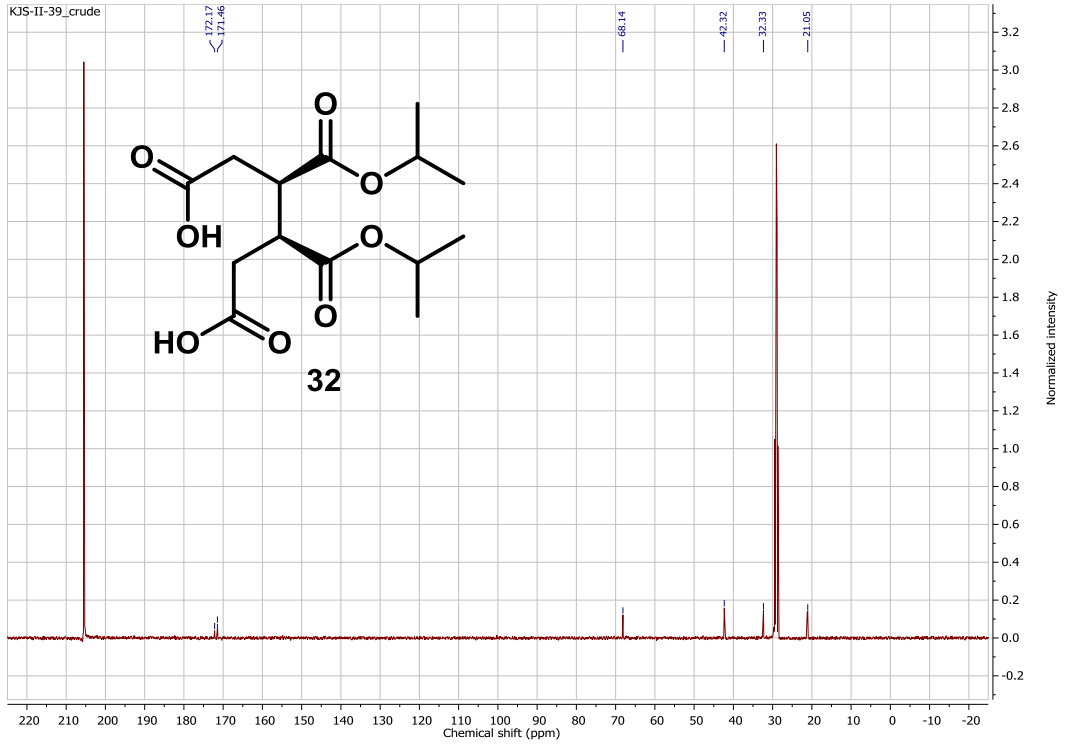
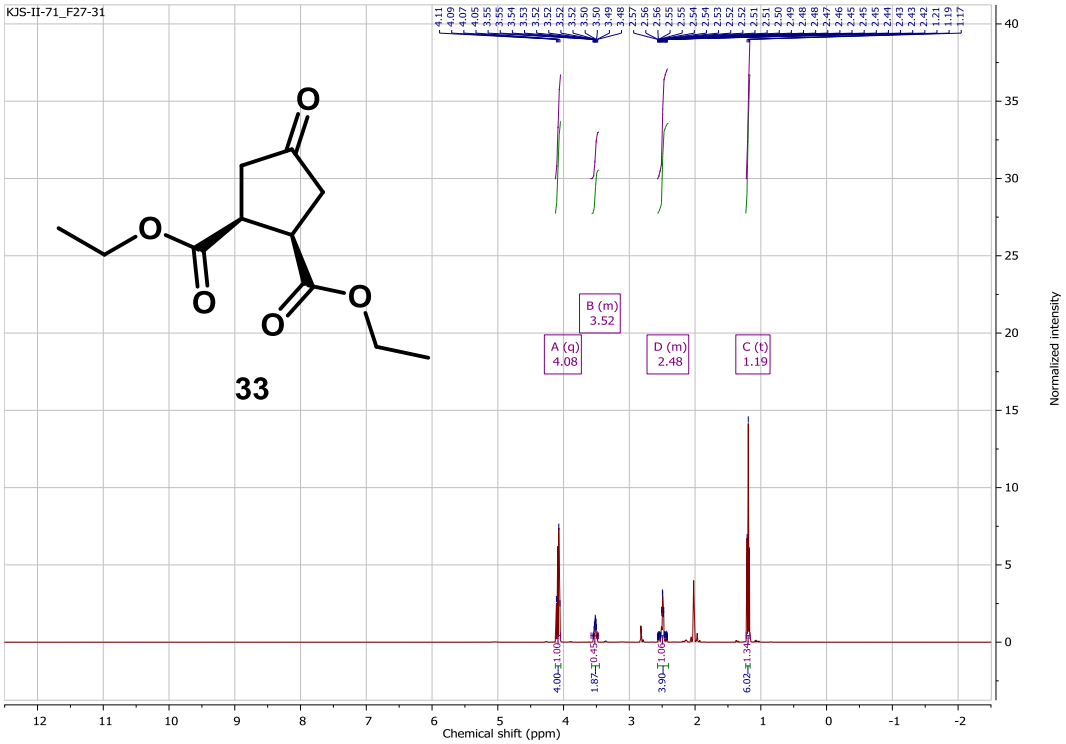
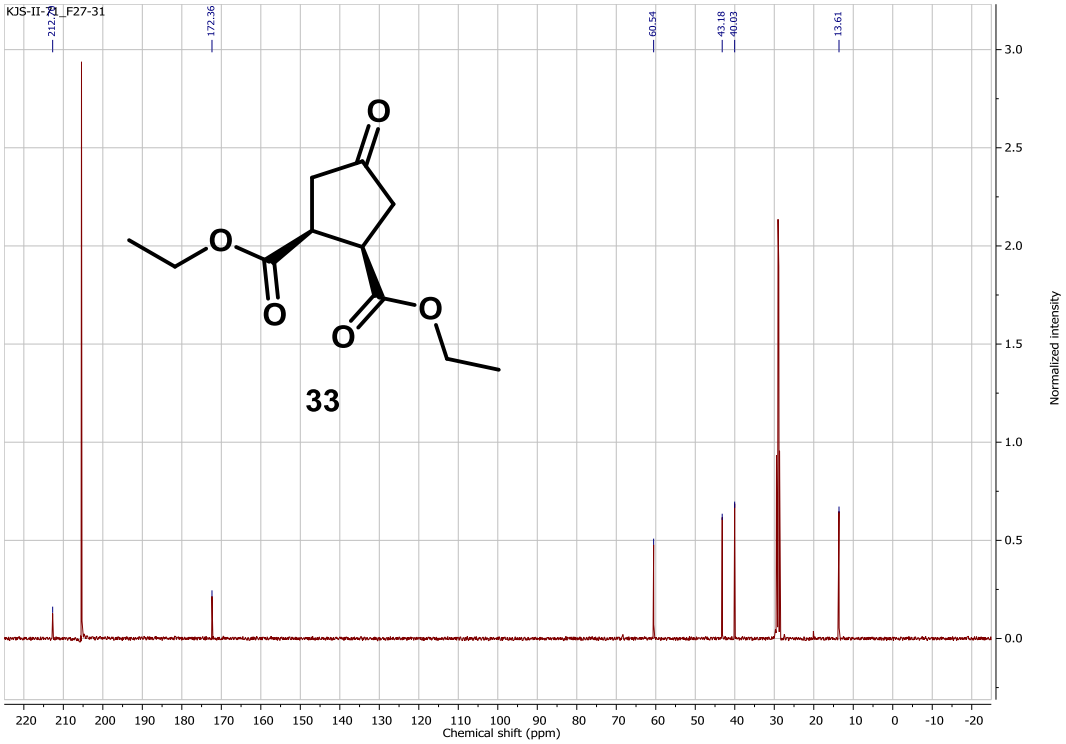
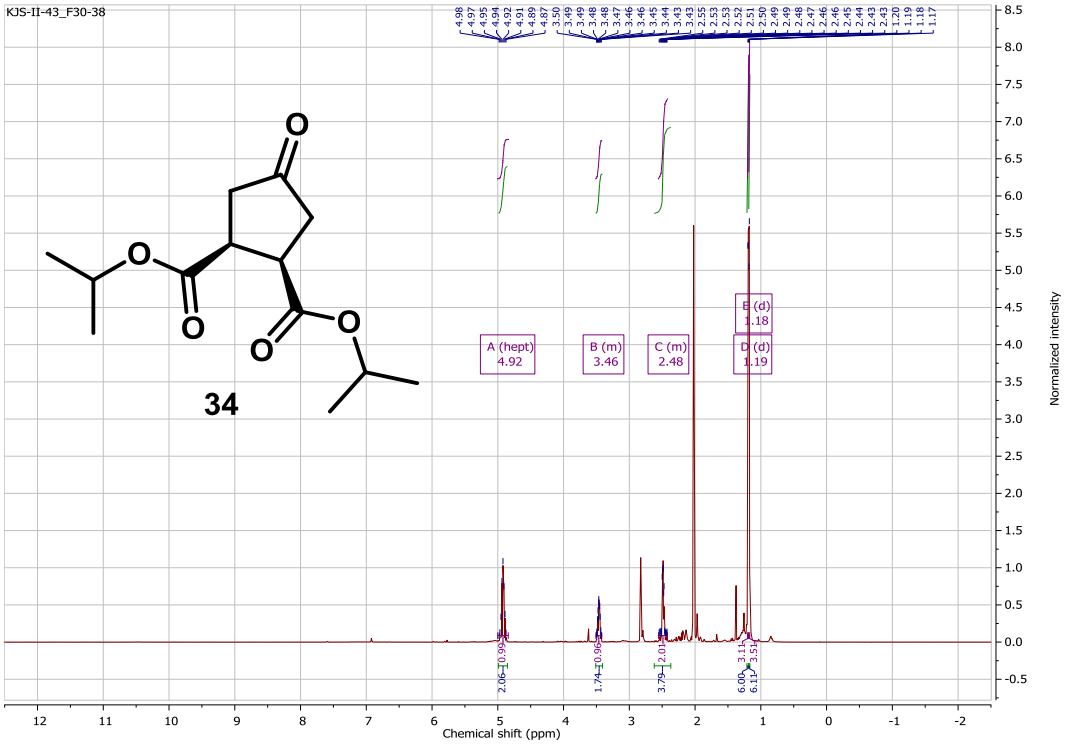
172.11
171.97
60.57
42.27
32.27
13.56
31
Chemical shift (ppm)
Normalized intensity

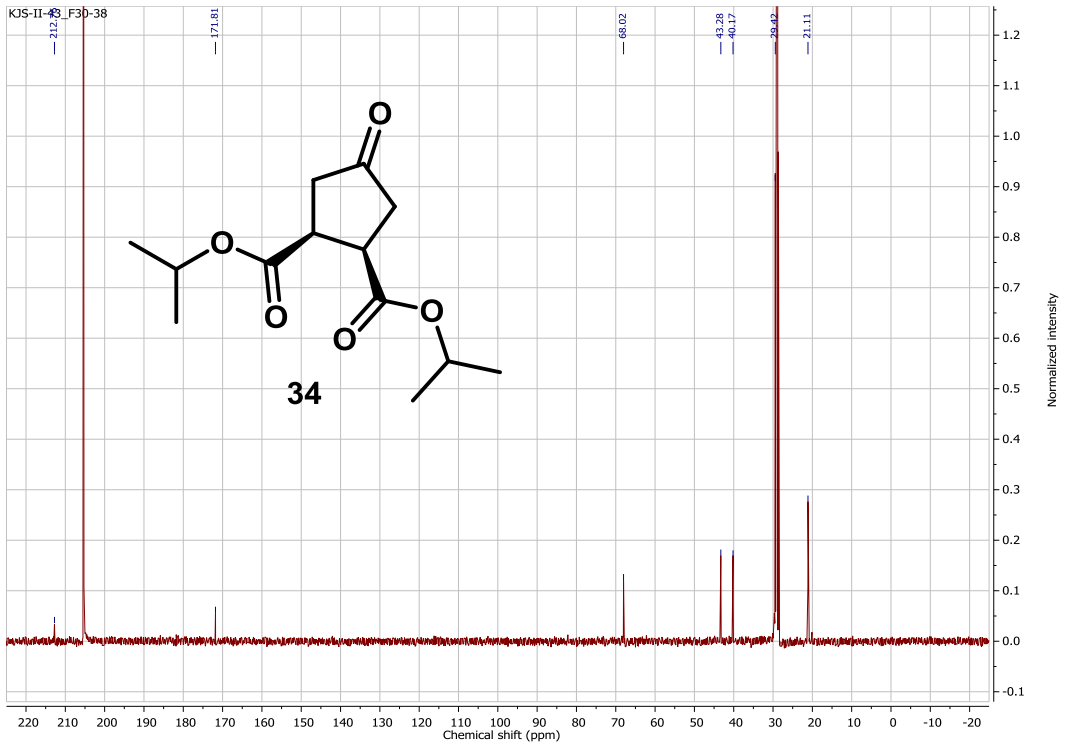

KJS-II-39_crude
32
A (sept) 4.94
B (m) 3.20
C (dd) 2.48
D (m) 2.71
E (d) 1.20
F (d) 1.18
Chemical shift (ppm)
Normalized intensity

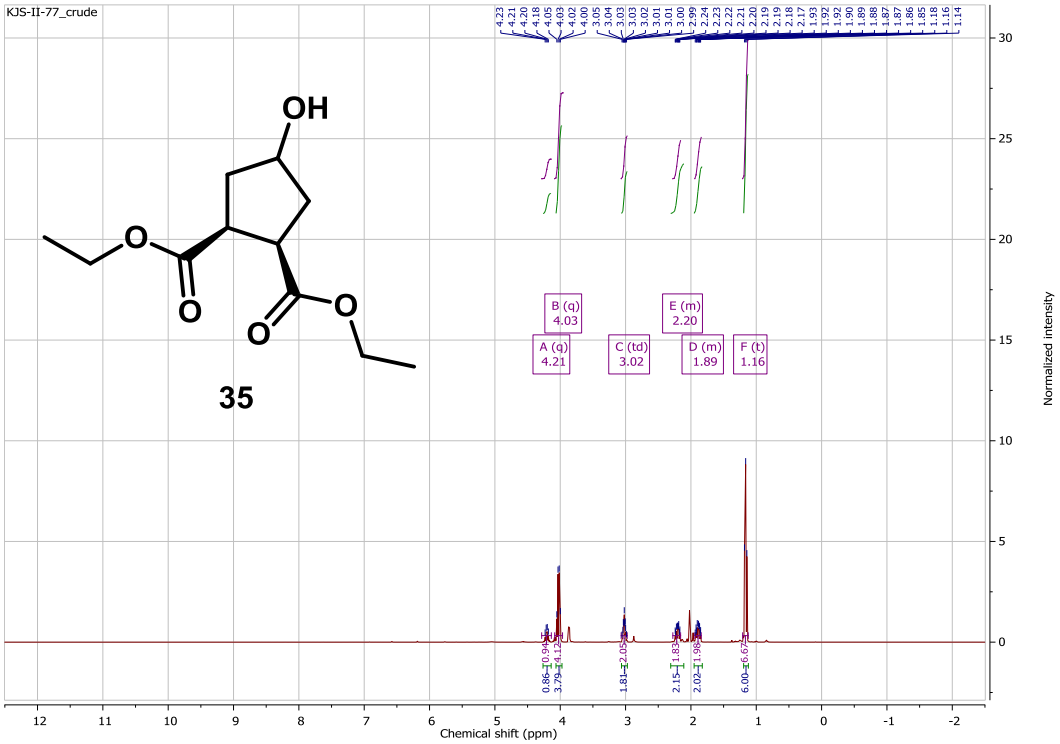

KJS-II-39_crude
172.17
171.46
68.14
42.32
32.33
21.05
32
Chemical shift (ppm)
Normalized intensity


KJS-II-71_F27-31
B (m)
3.52
A (q)
4.08
D (m)
2.48
C (t)
1.19
33
Chemical shift (ppm)
Normalized intensity


KJS-II-71_F27-31
212.21
172.36
60.54
43.18
40.03
13.61
33
Chemical shift (ppm)
Normalized intensity


KJS-II-43_F30-38
34
A (hept) 4.92
B (m) 3.46
C (m) 2.48
D (d) 1.19
E (d) 1.18
Chemical shift (ppm)
Normalized intensity


KJS-II-43_F30-38
212.73
171.81
68.02
43.28
40.17
29.42
21.11
34
Chemical shift (ppm)
Normalized intensity


KJS-II-77_crude
OH
O
O
O
O
35
B (q)
4.03
E (m)
2.20
A (q)
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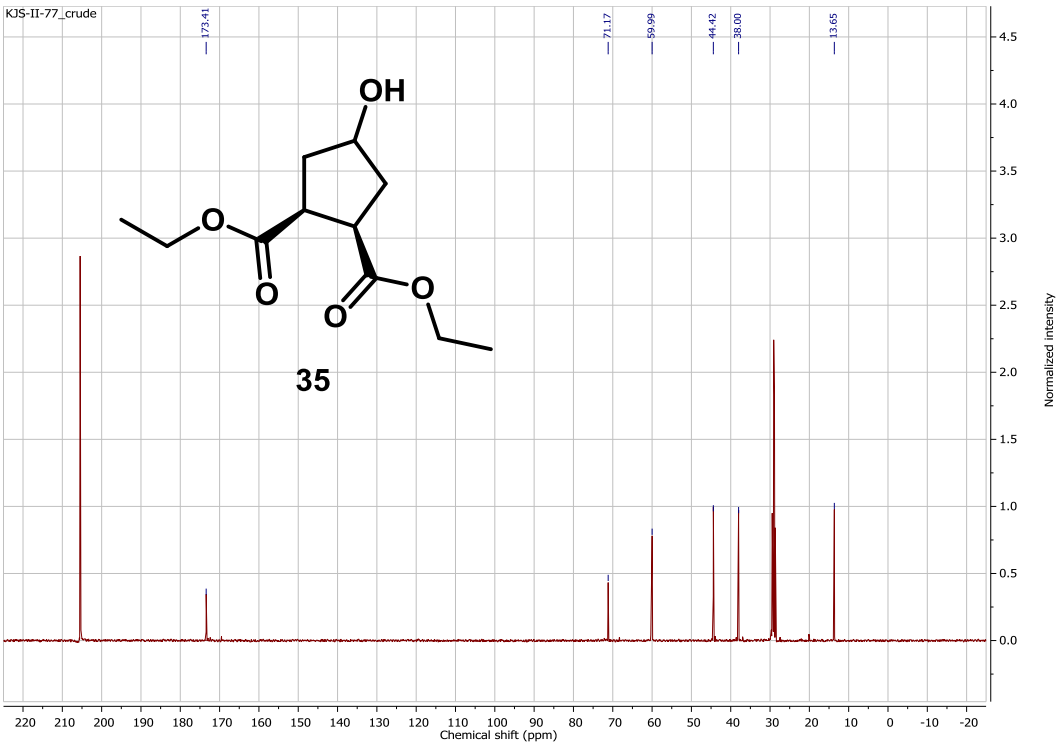
C (td)
3.02
D (m)
1.89
F (t)
1.16
Chemical shift (ppm)
Normalized intensity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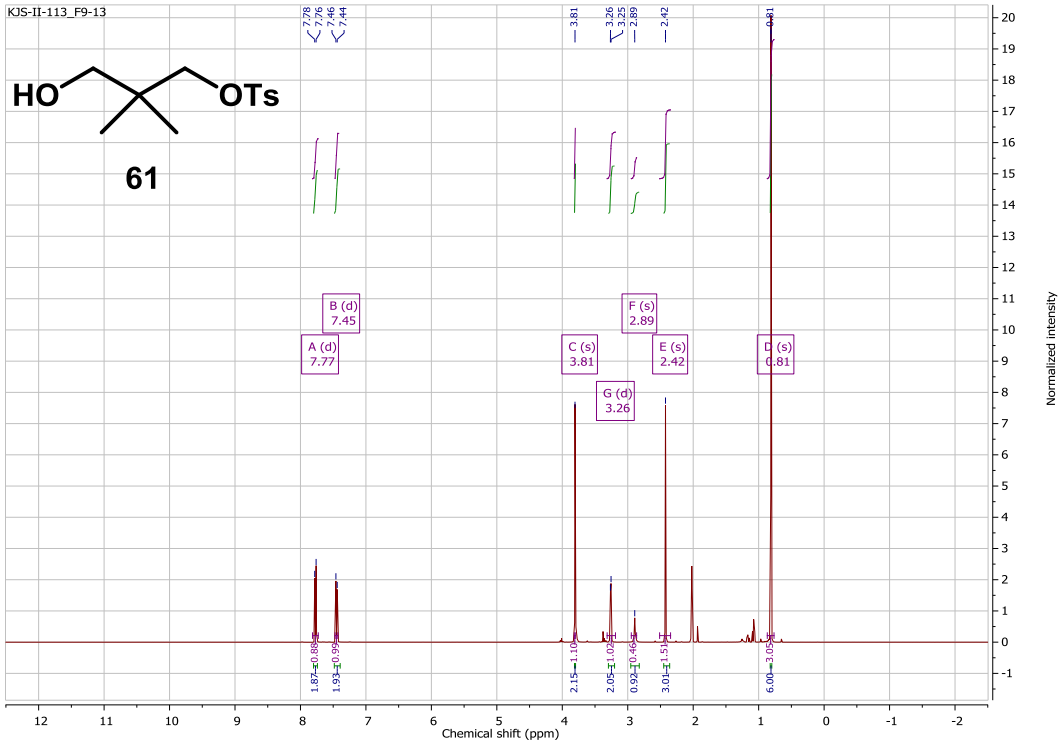
71.17
59.99
44.42
38.00
13.65
OH
O
O
O
O
35
Chemical shift (ppm)
Normalized intensity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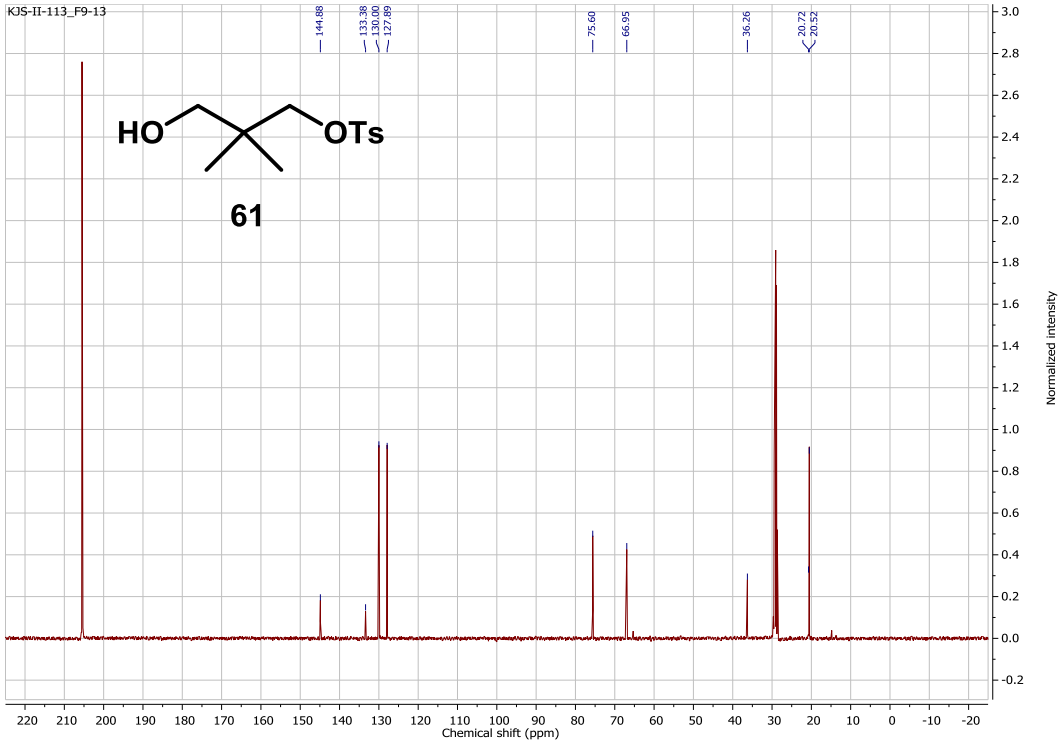
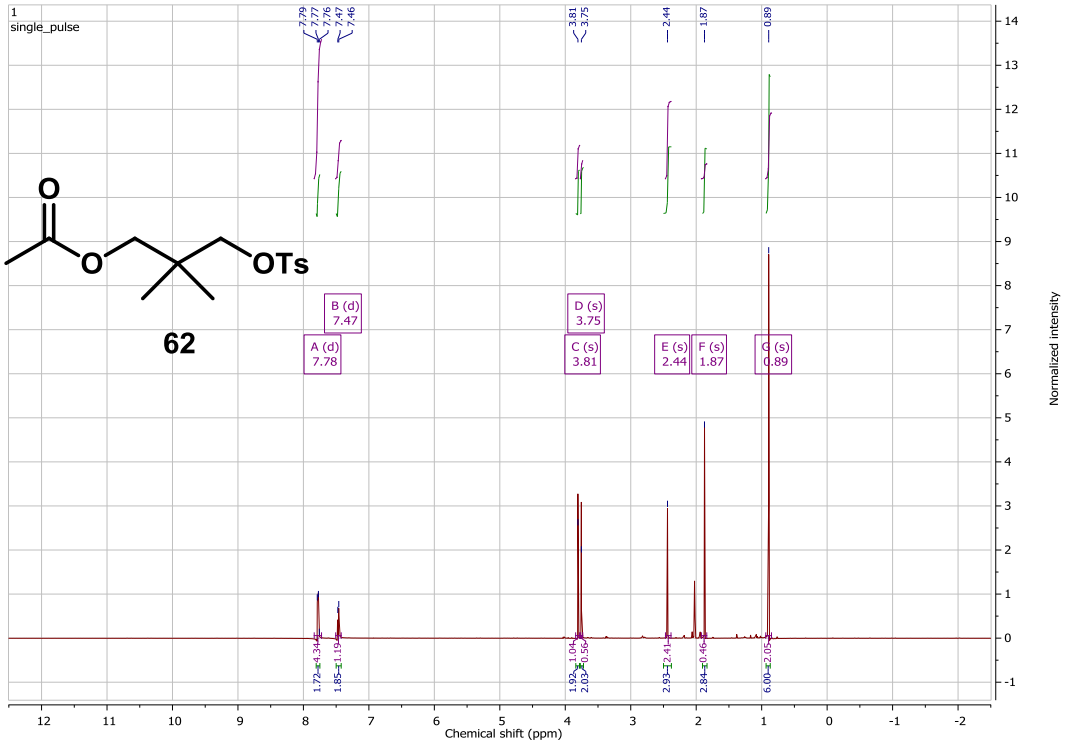
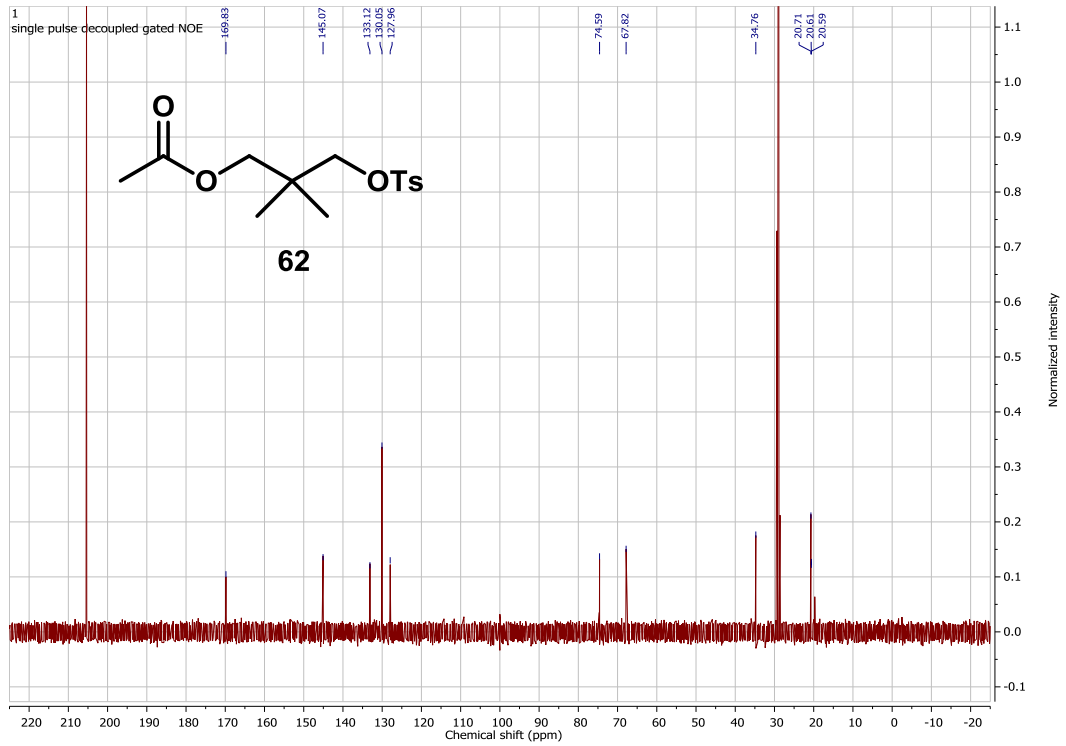
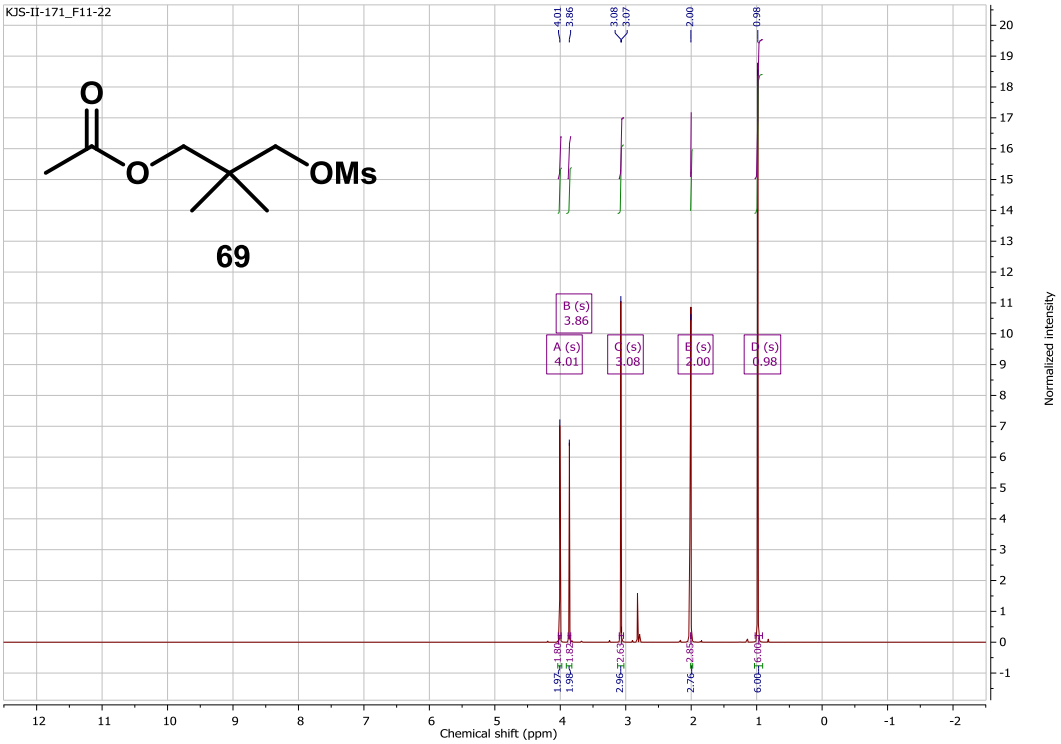
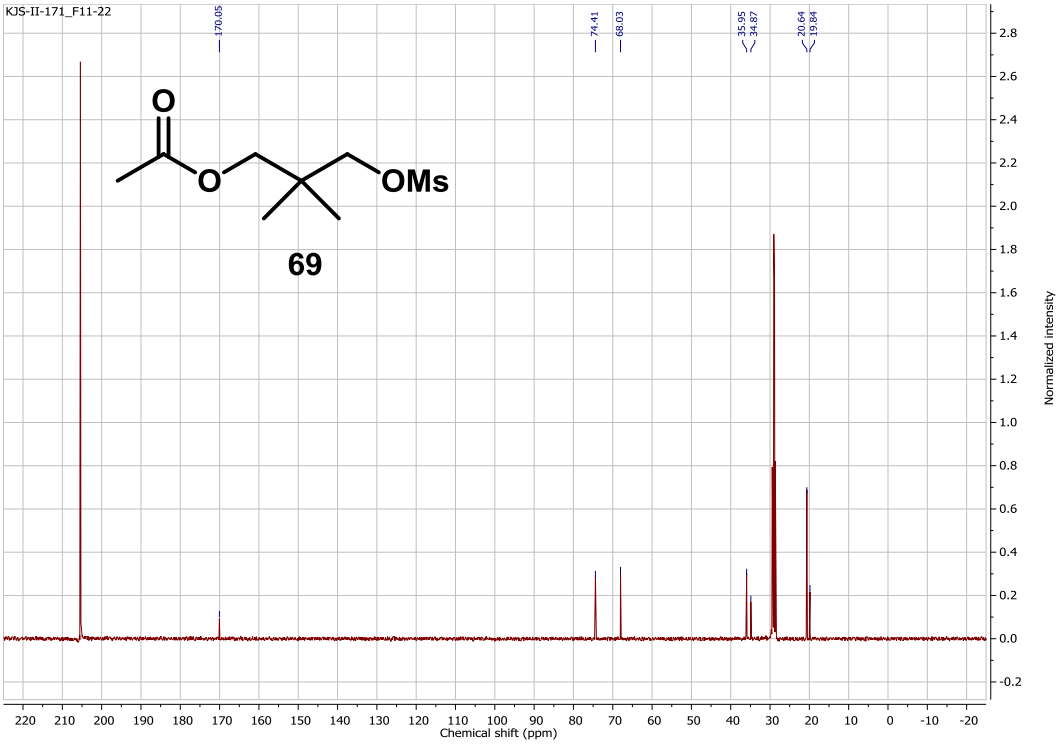
HO
OTs
61
B (d)
7.45
A (d)
7.77
F (s)
2.89
C (s)
3.81
E (s)
2.42
G (d)
3.26
D (s)
0.81
Chemical shift (ppm)
Normalized intensity

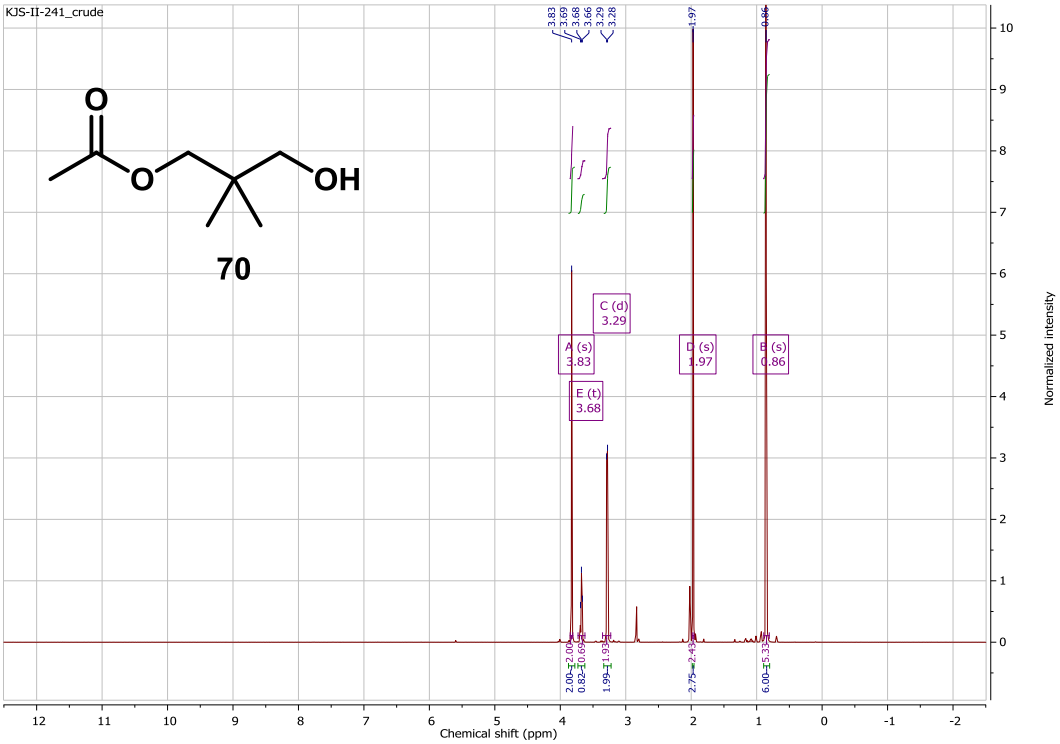

KJS-II-113_F9-13
HO
OTs
61
Chemical shift (ppm)
Normalized intensity

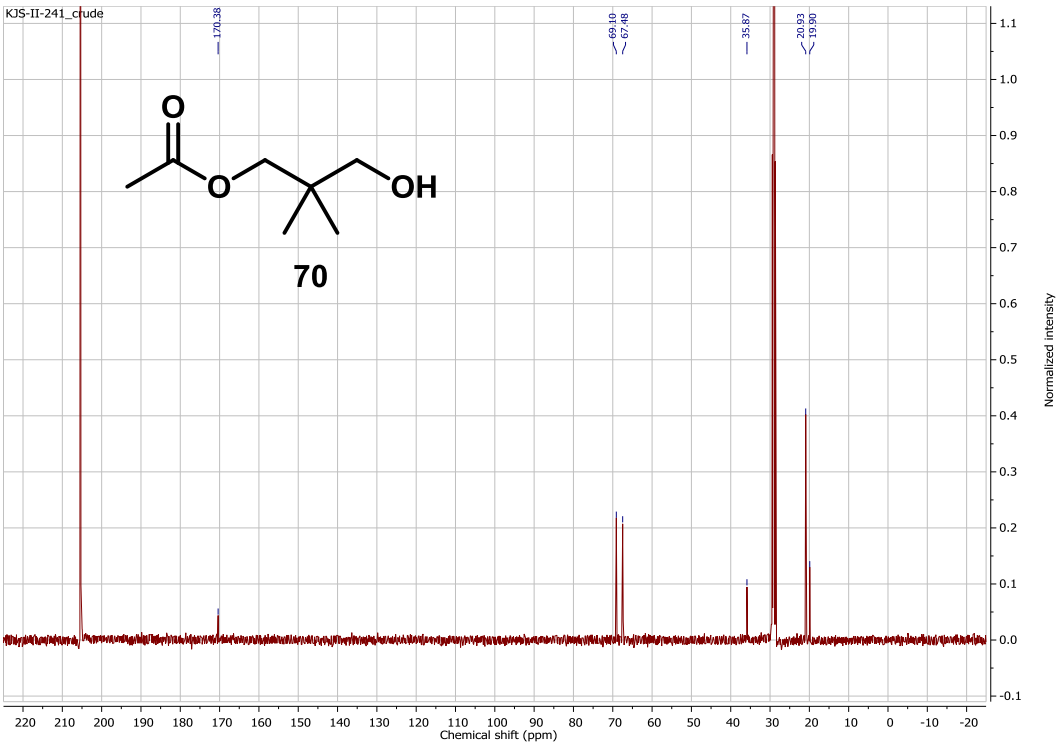

1
single_pulse
7.79
7.77
7.76
7.47
7.46
3.81
3.75
2.44
1.87
0.89
O
O
OTs
62
B (d)
7.47
A (d)
7.78
D (s)
3.75
C (s)
3.81
E (s)
2.44
F (s)
1.87
G (s)
0.89
1.72
4.34
1.85
1.19
1.92
1.04
2.03
0.56
2.93
2.41
2.84
0.46
6.00
2.05
Chemical shift (ppm)
Normalized intensity

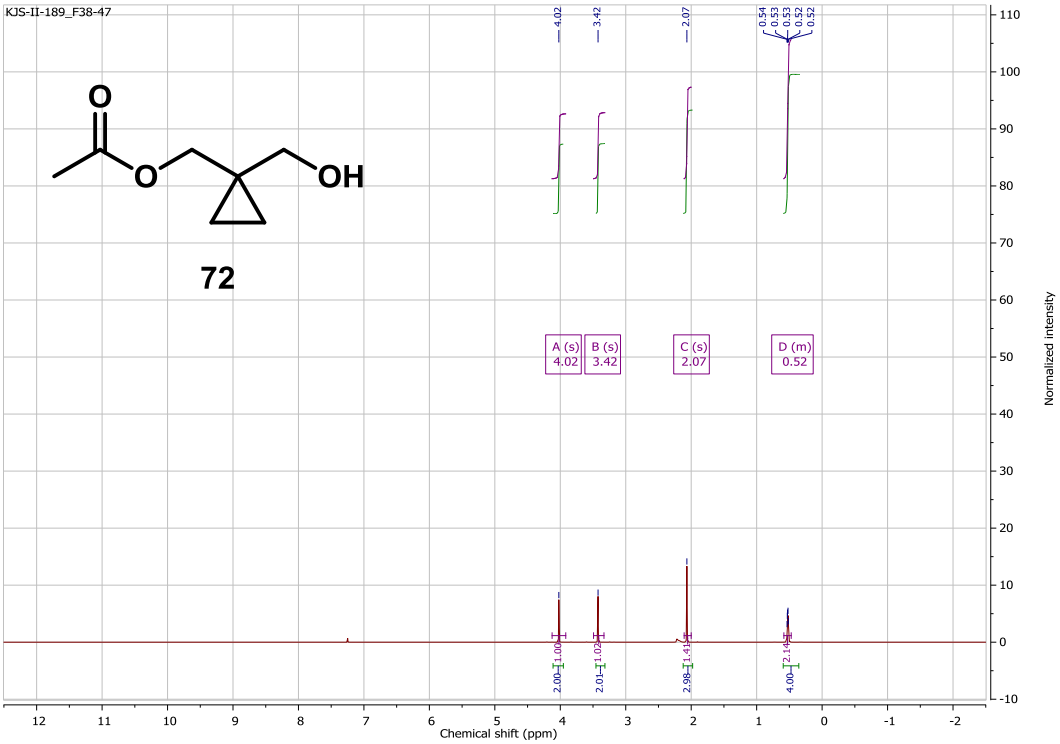

1
single pulse decoupled gated NOE
169.83
145.07
133.12
130.05
127.96
74.59
67.82
34.76
20.71
20.61
20.59
O
O
OTs
62
Chemical shift (ppm)
Normalized intensity

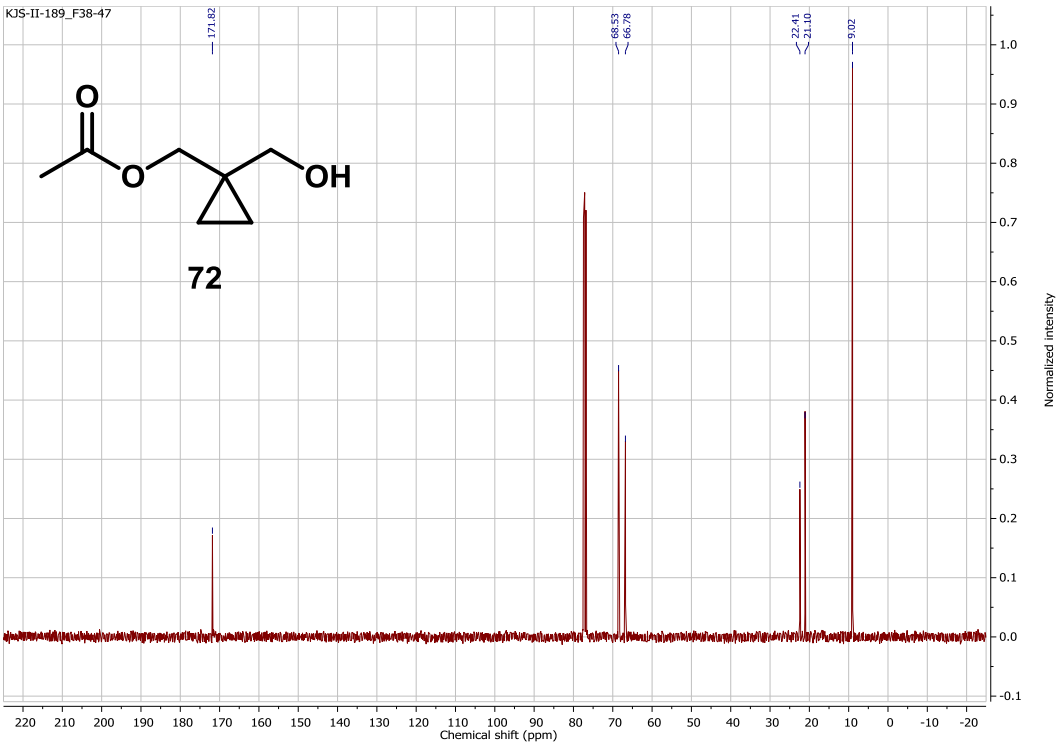

KJS-II-171_F11-22
O
O
OMs
69
4.01
3.86
3.08
3.07
2.00
0.98
B (s)
3.86
A (s)
4.01
C (s)
3.08
E (s)
2.00
D (s)
0.98
Chemical shift (ppm)
Normalized intensity

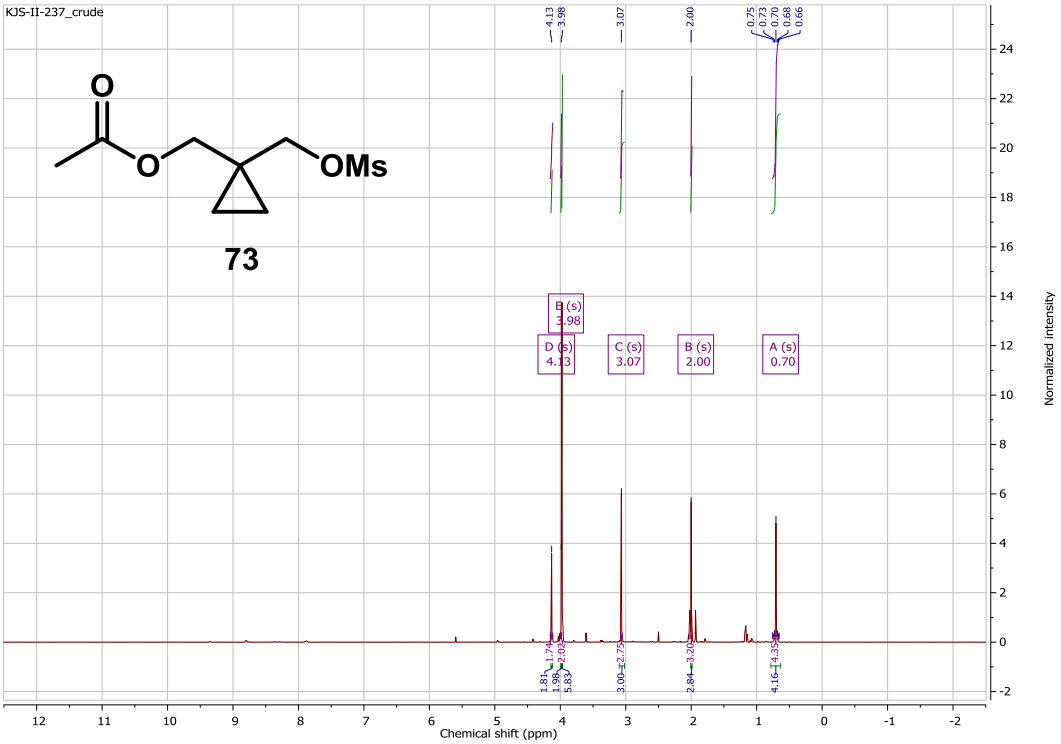

KJS-II-171_F11-22
170.05
74.41
68.03
35.95
34.87
20.64
19.84
O
O
OMs
69
Chemical shift (ppm)
Normalized intensity

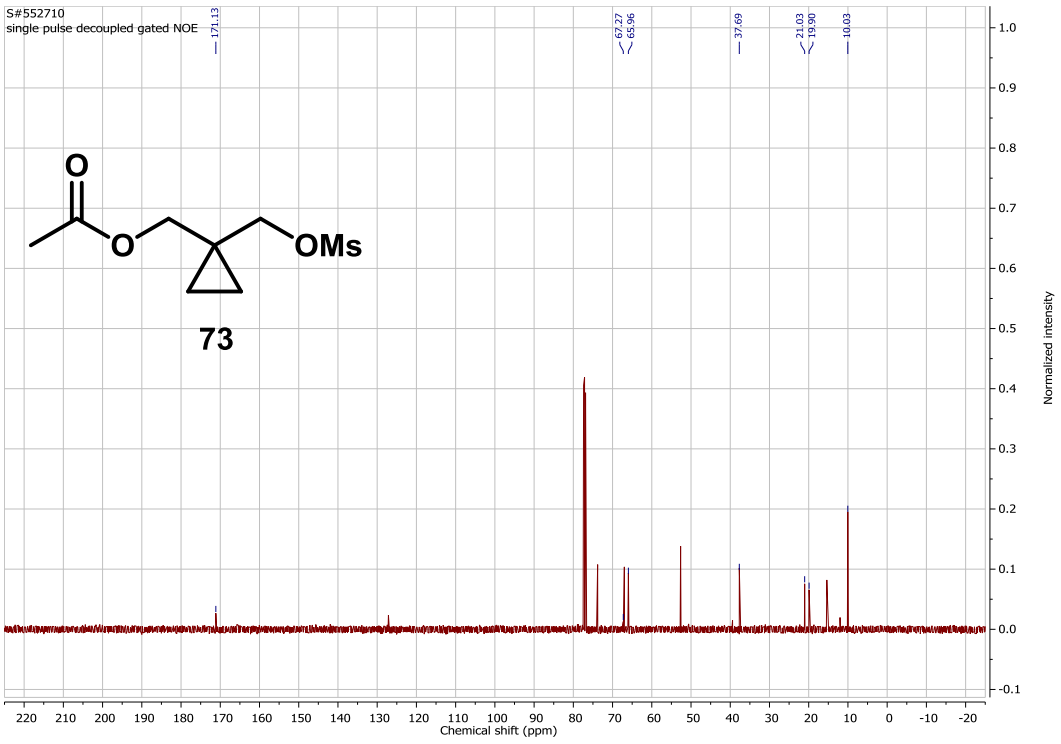

KJS-II-241_crude
O
O
OH
70
C (d)
3.29
A (s)
3.83
E (t)
3.68
D (s)
1.97
B (s)
0.86
Chemical shift (ppm)
Normalized intensity

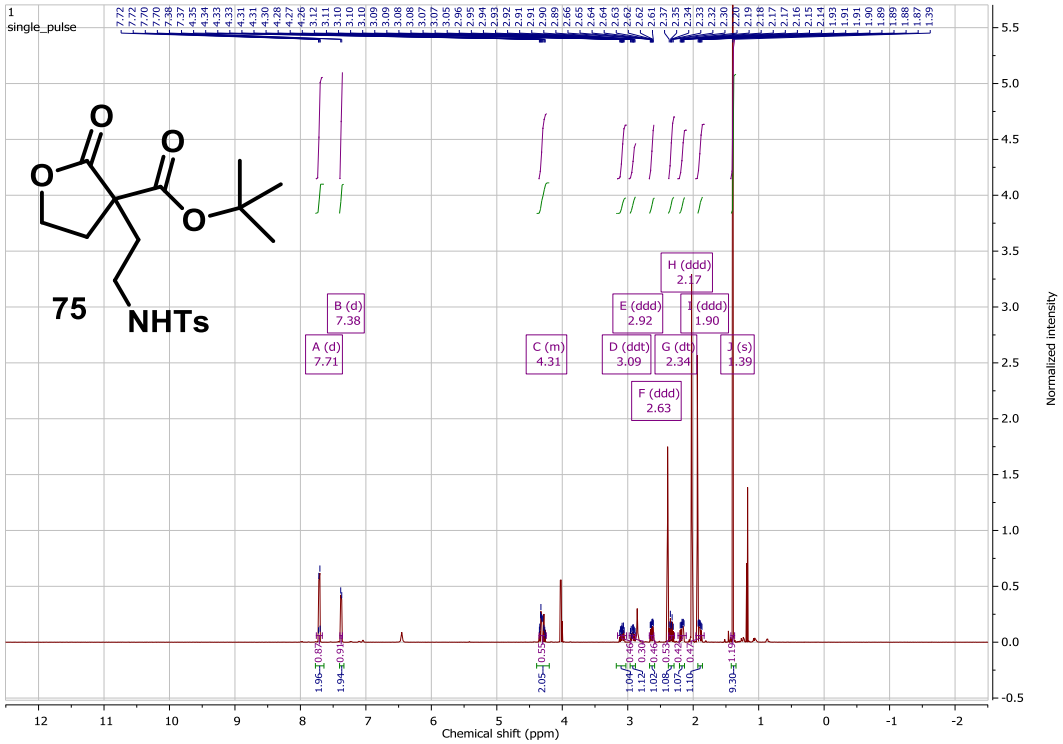

KJS-II-241_crude
170.38
69.10
67.48
35.87
20.93
19.90
O
O
OH
70
Chemical shift (ppm)
Normalized intensity

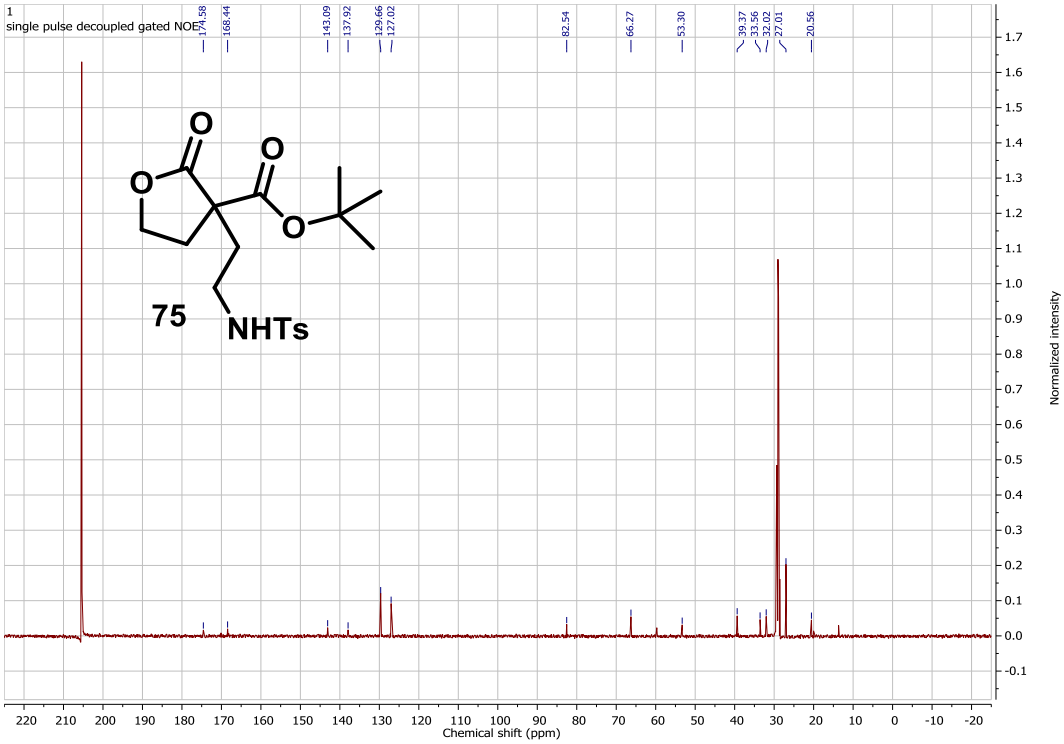

KJS-II-189_F38-47
O
O
OH
72
4.02
3.42
2.07
0.54
0.53
0.53
0.53
0.52
A (s)
4.02
B (s)
3.42
C (s)
2.07
D (m)
0.52
2.00
1.00
2.01
1.02
2.98
1.41
4.00
2.14
Chemical shift (ppm)
Normalized intensity

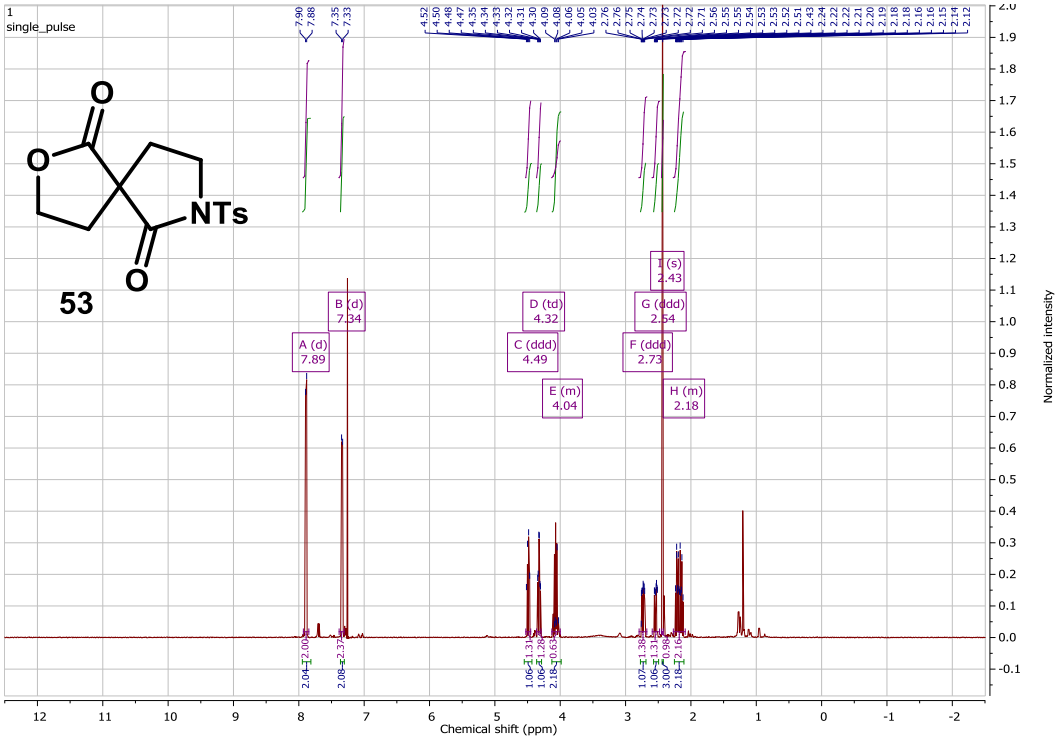

KJS-II-189_F38-47
O
O
OH
72
171.82
68.53
66.78
22.41
21.10
9.02
Chemical shift (ppm)
Normalized intensity

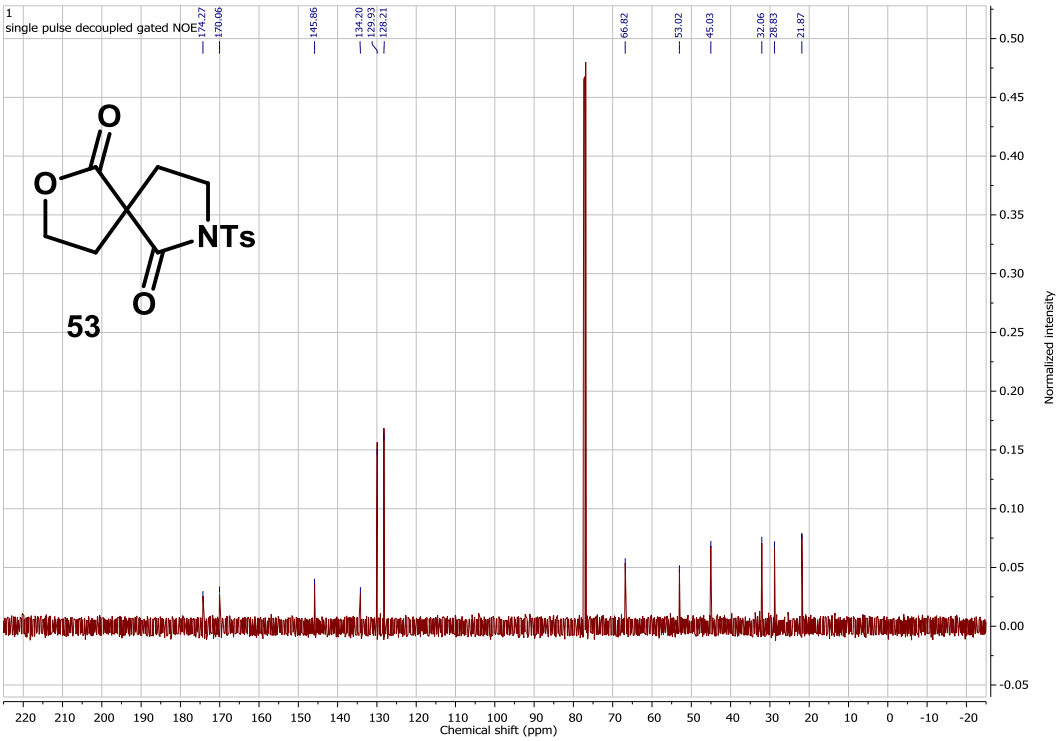

KJS-II-237_crude
O
O
OMs
73
4.13
3.98
3.07
2.00
0.75
0.73
0.70
0.68
0.66
B (s)
3.98
D (s)
4.13
C (s)
3.07
B (s)
2.00
A (s)
0.70
1.81
1.98
5.83
3.00
2.84
4.16
4.35
Chemical shift (ppm)
Normalized intensity

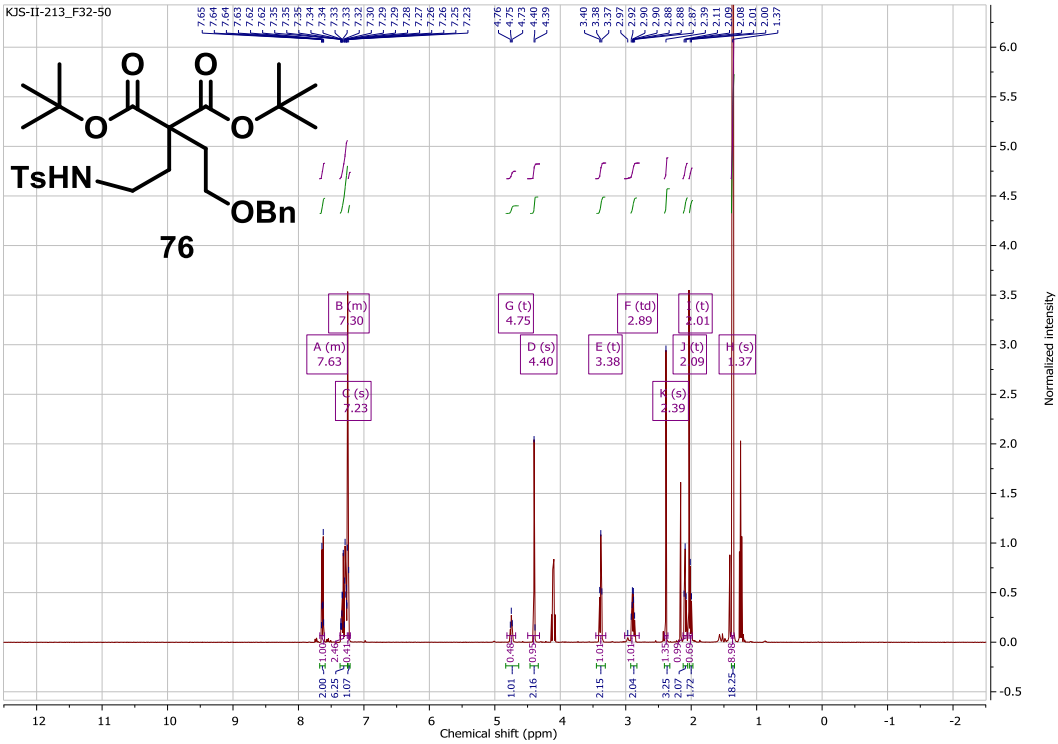

S#552710
single pulse decoupled gated NOE
171.13
67.27
65.96
37.69
21.03
19.90
10.03
O
O
OMs
73
Chemical shift (ppm)
Normalized intensity

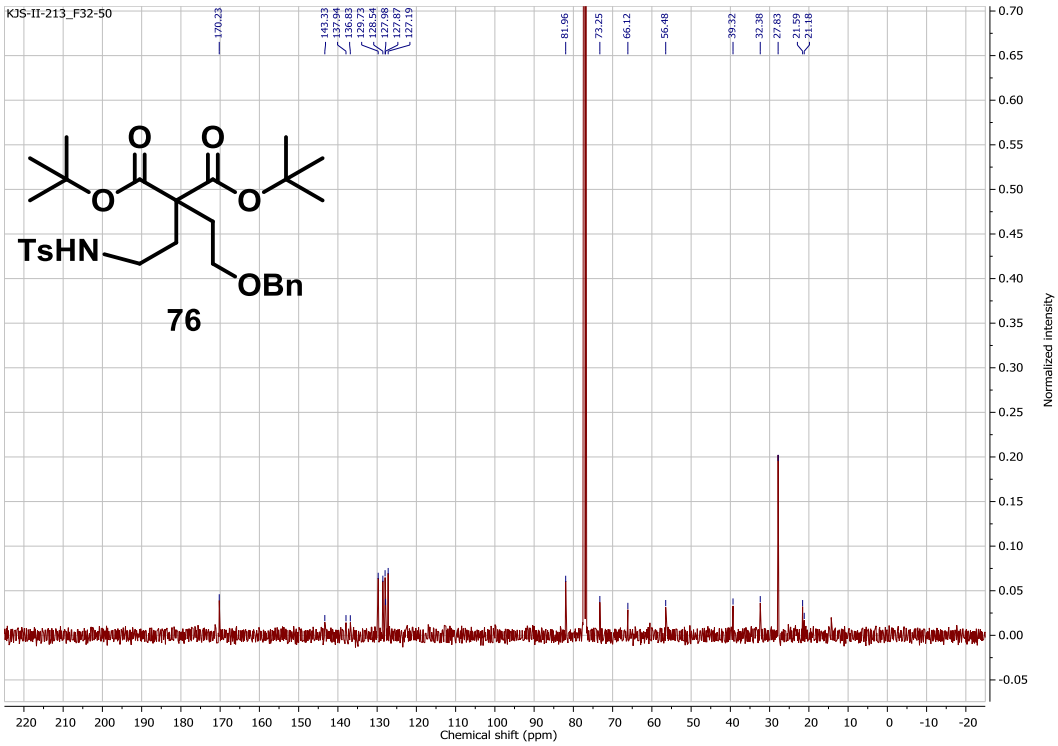

1
single_pulse
75
NHTs
A (d)
7.71
B (d)
7.38
C (m)
4.31
D (ddt)
3.09
E (ddd)
2.92
F (ddd)
2.63
G (dt)
2.34
H (ddd)
2.17
I (ddd)
1.90
J (s)
1.39
Chemical shift (ppm)
Normalized intensity

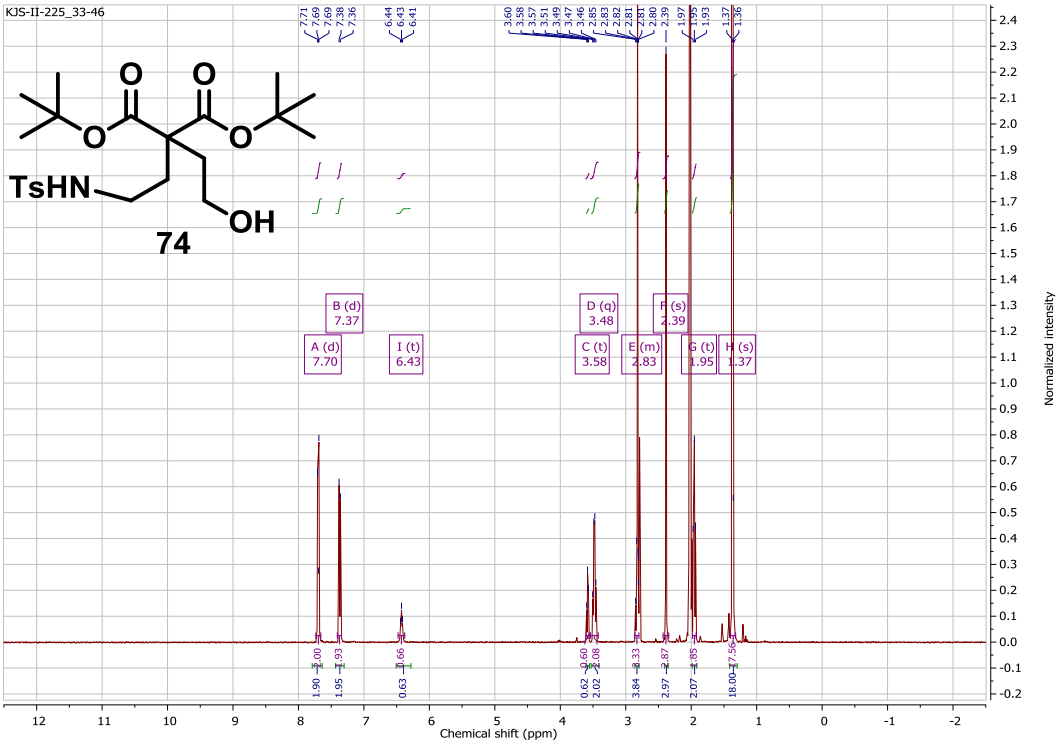

1
single pulse decoupled gated NOE
174.58
168.44
143.09
137.92
129.66
127.02
82.54
66.27
53.30
39.37
33.56
32.02
27.01
20.56
75
NHTs
Chemical shift (ppm)
Normalized intensity

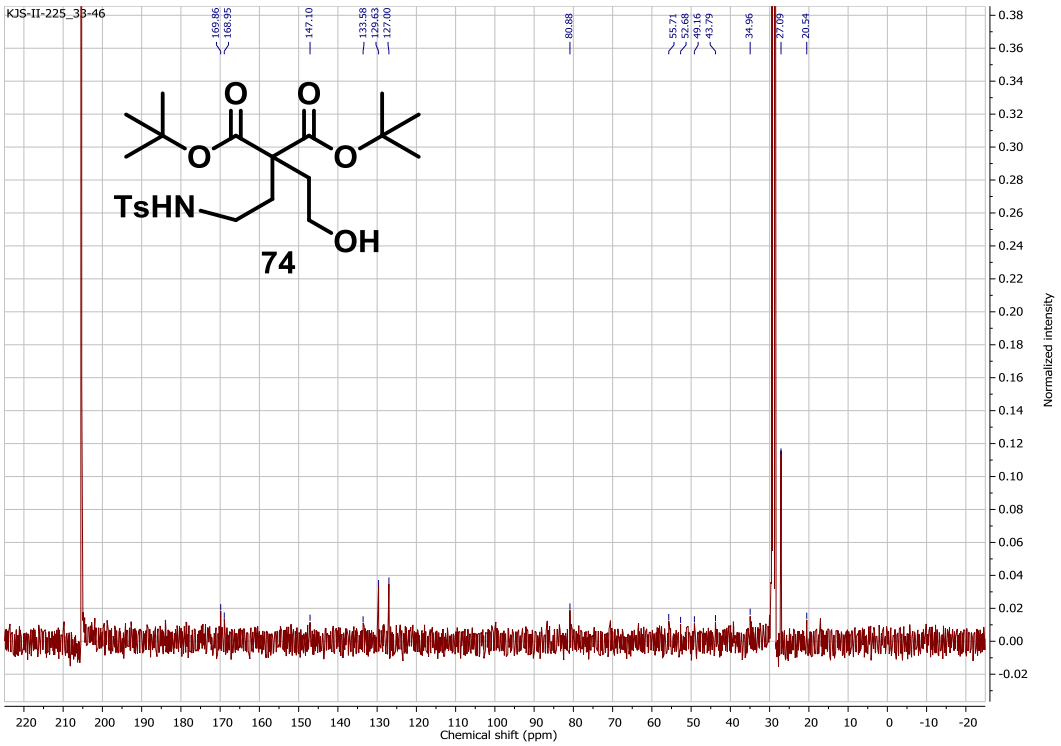

1
single_pulse
O
O
NTs
O
53
A (d)
7.89
B (d)
7.34
C (ddd)
4.49
D (td)
4.32
E (m)
4,04
F (ddd)
2.73
G (ddd)
2.54
I (s)
2.43
H (m)
2.18
Chemical shift (ppm)
Normalized intensity

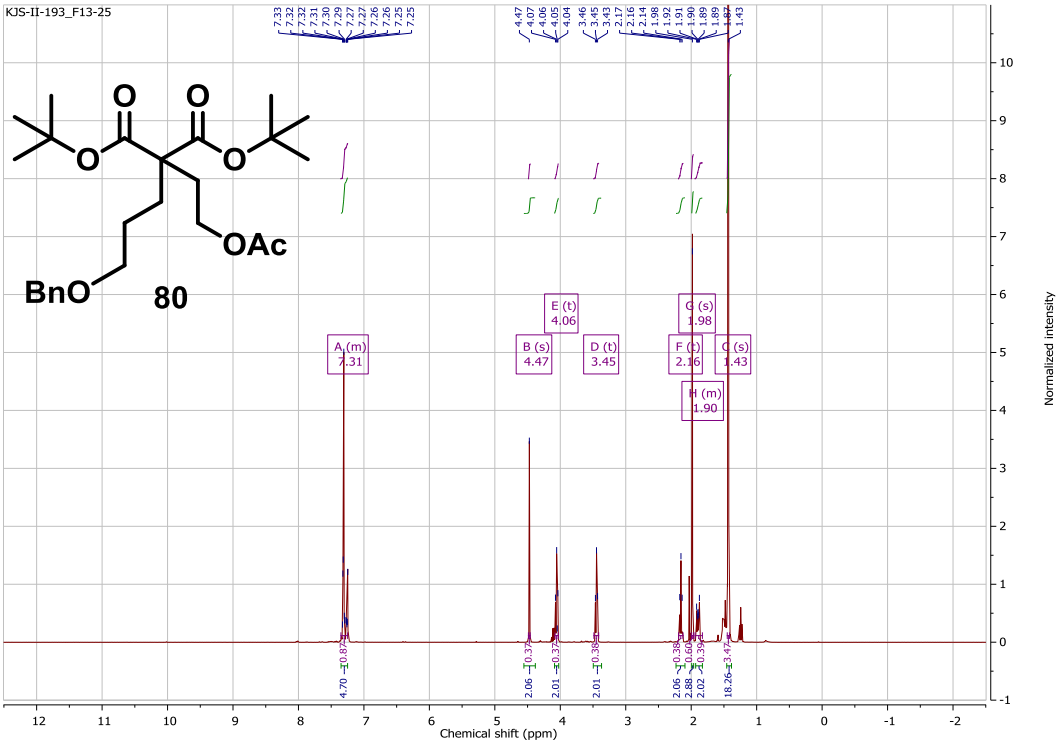

1
single pulse decoupled gated NOE
174.27
170.06
145.86
134.20
129.93
128.21
66.82
53.02
45.03
32.06
28.83
21.87
O
O
NTs
O
53
Chemical shift (ppm)
Normalized intensity

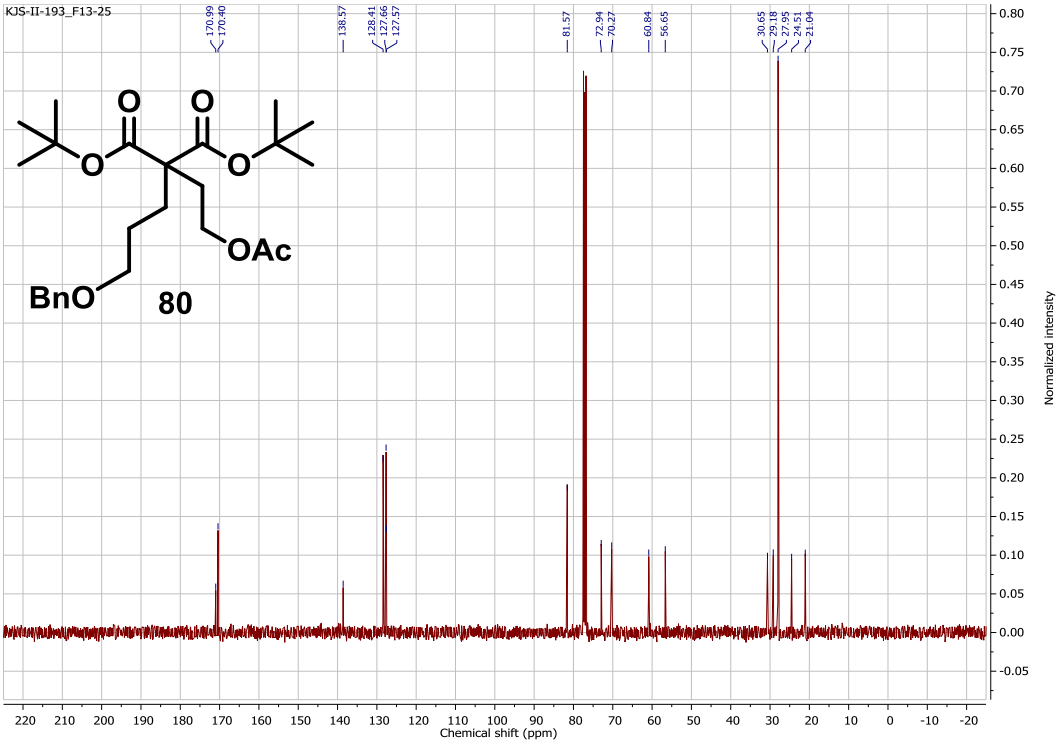

KJS-II-213_F32-50
TsHN
OBn
76
A (m) 7.63
B (m) 7.30
C (s) 7.23
D (s) 4.40
E (t) 3.38
F (td) 2.89
G (t) 4.75
H (s) 1.37
I (t) 2.01
J (t) 2.09
K (s) 2.39
Chemical shift (ppm)
Normalized intensity

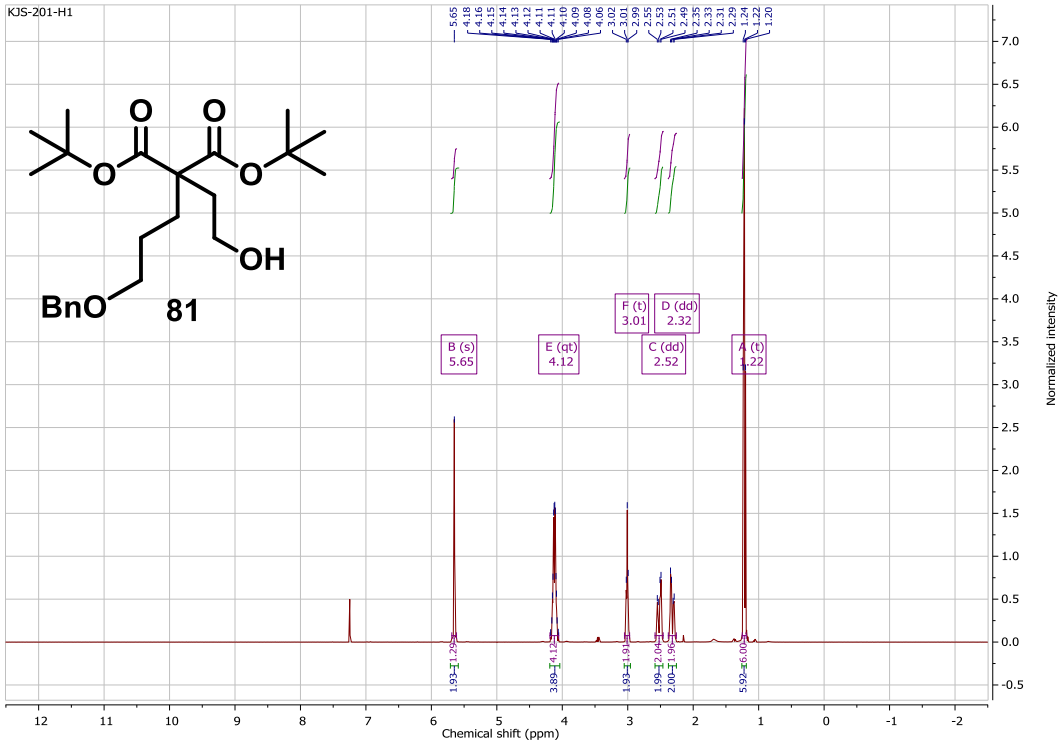

KJS-II-213_F32-50
TsHN
OBn
76
Chemical shift (ppm)
Normalized intensity

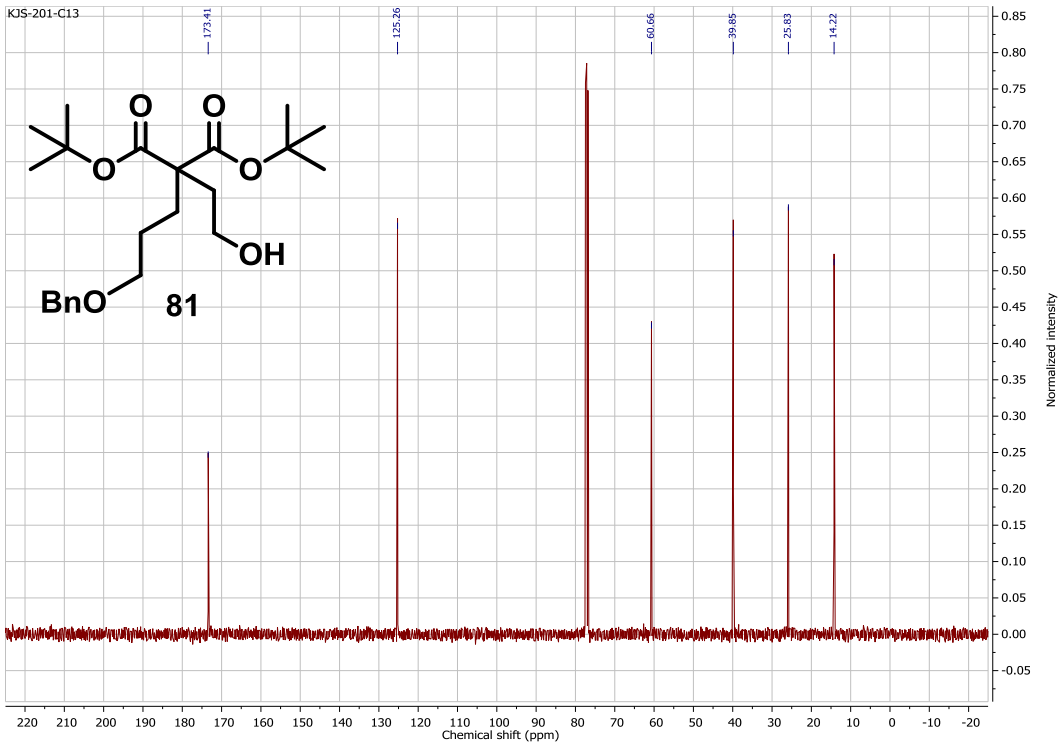

KJS-II-225_33-46
TsHN
OH
74
B (d) 7.37
A (d) 7.70
I (t) 6.43
D (q) 3.48
F (s) 2.39
C (t) 3.58
E (m) 2.83
G (t) 1.95
H (s) 1.37
Chemical shift (ppm)
Normalized intensity

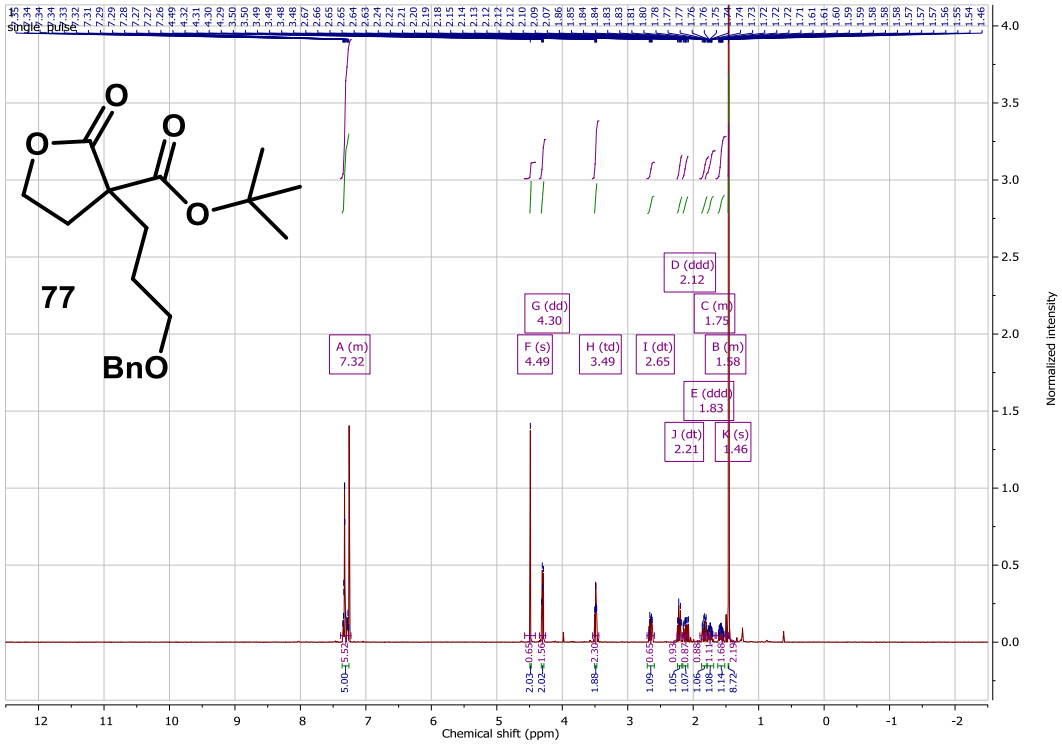

KJS-II-225_33-46
TsHN
OH
74
Chemical shift (ppm)
Normalized intensity

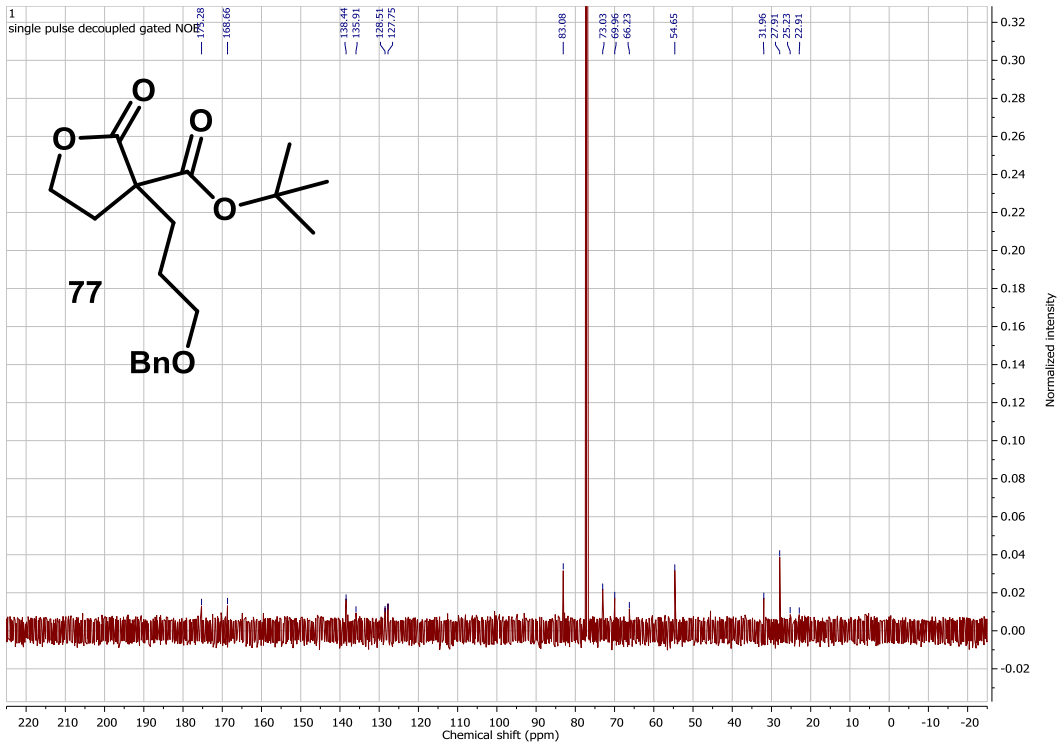

KJS-II-193_F13-25
OAc
BnO
80
A (m) 7.31
B (s) 4.47
D (t) 3.45
E (t) 4.06
F (t) 2.16
G (s) 1.98
C (s) 1.43
H (m) 1.90
Chemical shift (ppm)
Normalized intensity


KJS-II-193_F13-25
OAc
BnO
80
Chemical shift (ppm)
Normalized intensity


KJS-201-H1
BnO
OH
81
B (s) 5.65
E (qt) 4.12
F (t) 3.01
C (dd) 2.52
D (dd) 2.32
A (t) 1.22
Chemical shift (ppm)
Normalized intensity


KJS-201-C13
173.41
125.26
60.66
39.85
25.83
14.22
BnO
OH
81
Chemical shift (ppm)
Normalized intensity


single pulse
77
BnO
A (m) 7.32
F (s) 4.49
G (dd) 4.30
H (td) 3.49
I (dt) 2.65
D (ddd) 2.12
C (m) 1.75
B (m) 1.58
E (ddd) 1.83
J (dt) 2.21
K (s) 1.46
Chemical shift (ppm)
Normalized intensity


single pulse decoupled gated NOE
77
BnO
Chemical shift (ppm)
Normalized intensity